Universidade de Aveiro
Ano 2014

Secção Autónoma de Ciências da Saúde

DIANA ROCHA LOPES SILVA

CLINICAL RESEARCH IN COMMUNITY PHARMACIES – TRYING TO FIND A WAY

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Projeto apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizada sob a orientação científica do Professor Doutor Bruno Miguel Alves do Gago Professor Auxiliar Convidado da Secção Autónoma de Ciências da Saúde da Universidade de Aveiro

"Research is to see what everybody else has seen, and to think what nobody else has thought."

Albert Szent-Gyorgyi

o júri

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Agradecimentos

Estas páginas estariam em branco sem o contributo e precioso apoio de todos aqueles que comigo partilharam este caminho…

Agradeço ao Prof. Dr. Luís Almeida, pelo enorme entusiasmo com que me deu a conhecer este fascinante mundo que é a Biomedicina Farmacêutica. Pela ajuda na tentativa de encontrar o caminho, e pelo desafio que me propôs de realizar este trabalho.

Ao Prof. Dr. Bruno Gago, pelo apoio durante todo o mestrado, pela enorme disponibilidade e ajuda. E pela orientação e apoio na elaboração deste trabalho.

Aos colegas que tive o privilégio de conhecer durante este percurso. E aos amigos que me têm acompanhado!

À Susana e à Zulmira, por me fazerem sentir parte da equipa desde o primeiro momento, por todo o apoio e amizade!

Aos meus pais, o meu verdadeiro exemplo de força e determinação, que desde sempre me mostraram que tudo é possível, basta acreditarmos. São os meus ídolos!

Aos meus irmãos, Guido e Lucas, e à Patrícia, por tantas conversas, partilha de angústias, apoio e vontade de vencer!

Ao Nélio, meu amor e companheiro de todas as horas, por estar sempre presente e nunca me deixar desistir!

A todos, muito obrigada!

Palavras-chave Farmácia, Farmácia Comunitária, Farmacêutico, Investigação Clínica, Ensaio Clínico

Resumo

Este projeto propõe-se promover o envolvimento dos farmacêuticos de farmácia comunitária em investigação clínica. Nos últimos anos, a profissão farmacêutica tem passado por vários desafios. Ao mesmo tempo, os farmacêuticos têm procurado desenvolver um papel mais interventivo na comunidade. As competências que os farmacêuticos têm permitem-lhes um papel mais interventivo em investigação clínica, quer cooperando com as unidades de saúde, quer como investigadores. A proximidade ao utente e a inserção na comunidade, permite às farmácias comunitárias terem um papel importante em investigação clínica. A realidade portuguesa, até ao momento, não parece acompanhar a realidade doutros países neste âmbito. No entanto, Portugal reúne as condições necessárias para que essa realidade se altere. A crescente importância dos dados de vida real e o posicionamento das farmácias na comunidade deixam espaço para que a sua intervenção em investigação clínica possa ser melhorada. Assim, num futuro próximo será importante que as farmácias comunitárias sejam chamadas para esta realidade. Este projeto sugere a aplicação futura de um questionário de modo a avaliar a sua exequibilidade, avaliando o interesse das farmácias comunitárias portuguesas em investigação clínica e as possíveis barreiras à sua participação.

keywords Pharmacy, Community Pharmacy, Pharmacist, Clinical Research, Clinical Trial

abstract

This project aims to promote the involvement of community pharmacists in clinical research. In the last years, the pharmaceutical profession has gone through various challenges. At the same time, pharmacists have sought to develop a more active role in the community. The skills that pharmacists have allow them a more active role in clinical research, either cooperating with health units, either as researchers. The proximity to the patient and the placing in the community, allows community pharmacies to have an important role in the disclosure of clinical research. The Portuguese reality, so far, does not seem to reflect the reality of other countries in this field. However, Portugal has the necessary conditions for this situation to change. The growing importance of real world data and the placement of pharmacies in the community leave space for its involvement in clinical research to be improved. Thus, in the near future it would be important that community pharmacies are called upon to this reality. This project suggests the application of a questionnaire to Portuguese community pharmacies in order to assess the feasibility of this project, evaluating their interest in clinical research and identifying the possible barriers to their participation.

TABLE OF CONTENTS

FIGURES AND TABLES INDEX

ABBREVIATIONS AND ACRONYMS

AE	Adverse Event
ANF	*Associação Nacional das Farmácias* (National Association of Pharmacies)
APPE	Advanced Pharmacy Practice Experience
APSC	American Pharmacy Services Corporation
BLA	Biologics License Application
CEC	*Comissão de Ética Competente* (Competent Ethics Committee)
CEFAR	*Centro de Estudos e Avaliação em Saúde* (Centre for Health Evaluation & Research)
CEIC	*Comissão de Ética para a Investigação Clínica* (Ethics Committee for Clinical Research)
CES	*Comissão de Ética para a Saúde* (Ethics Committee for Health)
CISCRP	The Center for Information and Study on Clinical Research Participation
CNPD	*Comissão Nacional de Proteção de Dados* (National Committee for Data Protection)
COPD	Chronic Obstructive Pulmonary Disease
CPRN	Community Pharmacy Research Network
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CRO	Clinical Research Organisation
CTA	Clinical Trial Application
CTP	Clinical Trial Protocol
DeCS	Health Sciences Descriptors
DPI	Dry-Powder Inhaler
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FF/VI	Fluticasone Furoate/Vilanterol
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
Hb1Ac	Glycated Haemoglobin (Haemoglobin A1C)
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IVRS	Interactive Voice Response System

IWRS	Interactive Web Response System
LABA	Long-Acting β-Agonist
MA	Marketing Authorisation
MeSH	Medical Subject Headings
MHRA	Medicines and Healthcare products Regulatory Agency
MSC	Major Symptom Complex
NHP	Natural Health Product
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OF	*Ordem dos Farmacêuticos* (Pharmacists' Association)
OTC	Over the Counter
PPR	Pharmacy Practice Research
pRCT	Pragmatic Randomised Clinical Trial
PRODEFAR	Pharmaceutical Care Program for Pharmacological Treatment of Depression in Primary Care
R&D	Research & Development
RCT	Randomised Controlled Trials
RNEC	*Registo Nacional de Estudos Clínicos* (National Register of Clinical Studies)
SIR	Salford Integrated Record
SmPC	Summary of Product Characteristics
SONAR	Pharmacy Study Of Natural Health Product Adverse Reactions
SOP	Standard Operational Procedure
SWOT	Strengths, Weaknesses, Opportunities and Threats
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation

1. INTRODUCTION

Over the years, the profession of Pharmacy has begun to undertake major changes in practice. Driven by marketplace realities the profession has recognized the need to provide cognitive services either than the traditional role of product supply which has made pharmacists feel their skills as underused (1, 2).

The increased personal interest in these issues and the development of competences on clinical research during the curricular period of the Master course in Pharmaceutical Medicine led to develop the hypothesis of integrating both worlds.

The current paradigm of Portuguese healthcare and particularly the changes faced on the Community Pharmacy setting make it possible to understand recent initiatives of extending community pharmacists' role within this framework (2, 3). In order to increase pharmacist's interest in research and promote their involvement, there is a need to fully investigate the barriers and facilitators to this new role (1).

This project aims to show the international reality on this issue, in order to be the basis of further studies. It is intended that this work can be used as a guide and a facilitator for introducing clinical research, and clinical trials particularly, in the context of Portuguese community pharmacies.

1.1. OBJECTIVES

The information about clinical trials in a community pharmacy setting is limited in a global perspective and very scars when talking about the Portuguese reality. In an attempt to help fulfilling this gap the objective of this project is to identify the role pharmacists have and/or might have in clinical research; particularly, the potential role of community pharmacies in clinical trials.

A global revision on this subject will be presented in order to help to delineate a possible strategy that can help to enhance the role of Portuguese community pharmacies in clinical research in the future.

1.1.1. METHODS

This work consists in a review of international peer-reviewed literature on scientific databases ISI Web of Knowledge and PubMed using MeSH (Medical Subject Headings) and DeCS (Health Sciences Descriptors) terms “community pharmacies”, “clinical trial” and “clinical research”. Other main search term used was “pharmacist” due to its relevance for this study. The search was focused in publications of the last five years, although some older publications were also used due to its relevance for the study or because it is a primary source which should be cited. Clinicaltrials.gov and clinicaltrialsregister.eu were also consulted in order to find clinical studies in community pharmacies. The search was extended for English and Portuguese manuscripts, because it is the language of proficiency of the research team and of the target population.

Reference lists of retrieved studies were reviewed for relevant articles. Studies were assessed for relevance based on the abstracts. Relevance was judged by health improvement and the role of community pharmacy and community pharmacists, particularly. Manuscripts in which community pharmacy or community pharmacist were not a major heading were excluded.

Grey literature such as conference proceeding, abstracts, presentations and technical reports were identified on these topic using generic search engines (e.g. Google).

The findings are presented as a narrative summary.

1.1.2. STRUCTURE

To answer the issue in debate, it was necessary to verify the current situation (state of the art) of clinical research, particularly of clinical trials.

In attempt to positioning the community pharmacy in clinical research, it is described what has been done on this subject and in chapter 4 some real-life examples are shown.

In chapter 5 it was tried to transpose this kind of research to Portuguese reality and a brief description of the involved stakeholders is made. Then a suggestion is given: a questionnaire to be filled out by Portuguese pharmacies. This questionnaire lacks translation and validation to the Portuguese population; therefore, in this chapter Strengths, Weaknesses, Opportunities and Threats (SWOT) of its application are analysed.

In chapter 7, all data obtained are discussed and finally, in chapter 8 a conclusion of this project is presented.

2. CLINICAL RESEARCH OVERVIEW

Clinical research is research that directly involves a particular person, or group of individuals, or that uses materials from humans, such as their behaviour or tissue samples. Clinical trial defines a particular case of clinical research. It is any investigation in human subjects intended to discover or verify the clinical, pharmacological, pharmacokinetic or pharmacodynamic effects of an investigational medicinal product (IMP), or to identify any adverse reactions to an investigational medicinal product, with the objective of determine its safety and/or efficacy. (4, 5) Figure 1 shows several types of medical research.

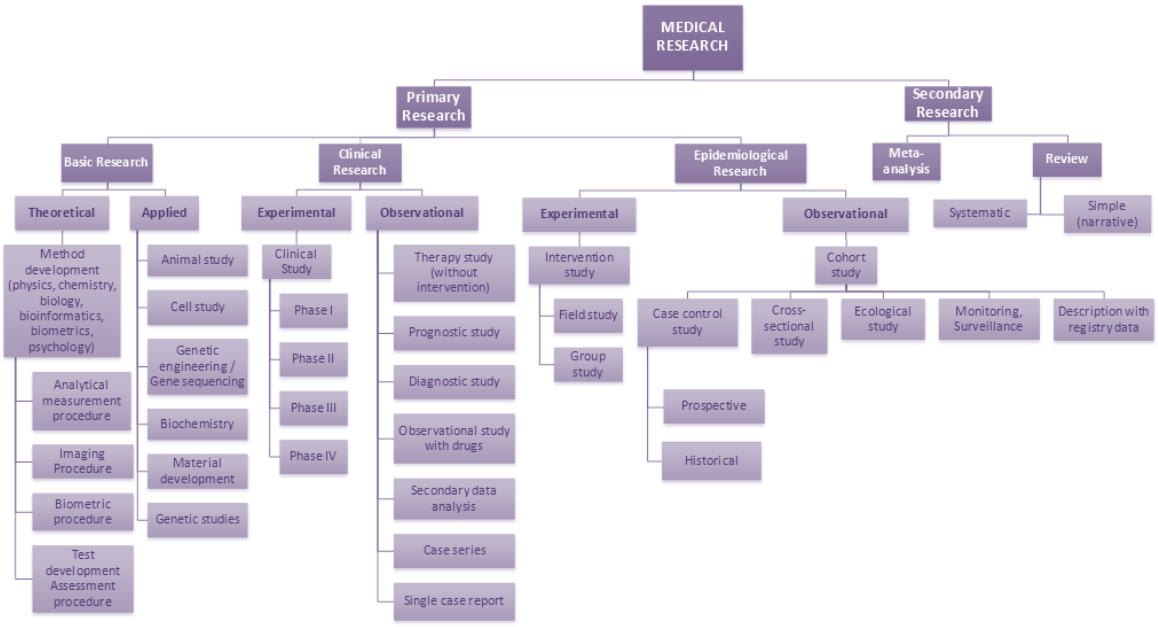

Figure 1. Classification of different study types (adapted from (5)).

2.1. CLINICAL TRIALS - CONTEXT

It may never be known for certain who carried out the first controlled clinical trial. According to the written history, James Lind is considered the “father” of modern clinical trials, since he was the first one to conduct a recorded controlled clinical trial, in 1947. In 1753, he published his account of a trial of six potential remedies for scurvy. He allocated two scorbutic sailors to each treatment: cider, sulphuric acid, vinegar, seawater, nutmeg paste with barley water, or citrus fruit (two oranges and one lemon), once daily. This was

an open trial, had no placebo arm, used only 12 patients and it cost almost nothing; yet it led to profound and permanent changes in clinical practice and in health of countless people (6). About 50 years later came what might be the first placebo-controlled double-blind clinical trial (7).

Medicines were not subjected to systematic trial until the 20th century, even though powerful and effective preparations had by then been in use for millennia (7).

The first large-scale randomised controlled clinical trial is generally recognised to be the United Kingdom (UK) Medical Research Council's comparison of streptomycin plus bed rest with bed rest alone, in the treatment of pulmonary tuberculosis (8, 7). This trial which began recruiting patients in 1947 and whose results were published in 1948 became a landmark in the development of clinical trial methodology, because of its inclusion of a "best existing treatment" control group, its carefully organisation and its use of sealed randomisation envelopes (7).

These characteristics (use of control groups, randomisation and blinding) have become essential for the results of an interventional clinical study to be realistic.

In this way, 1990 is also a milestone in the history of clinical research. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was assembled to help eliminate differences in drug development requirements for the three global pharmaceutical markets: European Union (EU), United States of America (USA) and Japan. The birth of ICH took place at a meeting in April 1990, hosted by European Federation of Pharmaceutical Industries and Associations (EFPIA) in Brussels. Representatives of the regulatory agencies and industry associations of Europe, USA and Japan met primarily to plan an International Conference. However, in this meeting wider implications and terms of reference of ICH were also discussed. The ICH initiatives promote increased efficiency in the development of new drugs, improving their availability to patients (9).

ICH stands Good Clinical Practice (GCP) guidelines whose principles represent agreed scientific guidance for meeting technical registration within the three ICH regions. The ICH Guidelines are not intended to be comprehensive guidance covering all aspects of product development and registration. Instead of this, they are intended to be used in combination with any regional requirements (9). Thus, ICH Guidelines objective is to standardize the conduction of clinical trials in accordance with GCP.

In the end of the day, ICH GCP Guidelines seek the development of drugs with Quality, Safety and Efficacy (*cf.* Figure 2).

Figure 2. Standards in Clinical Development.

2.2. Clinical Trials Key Stakeholders

The complexity of clinical trials associated to research and development of new medicines, implies the involvement of several stakeholders as described below (7, 10).

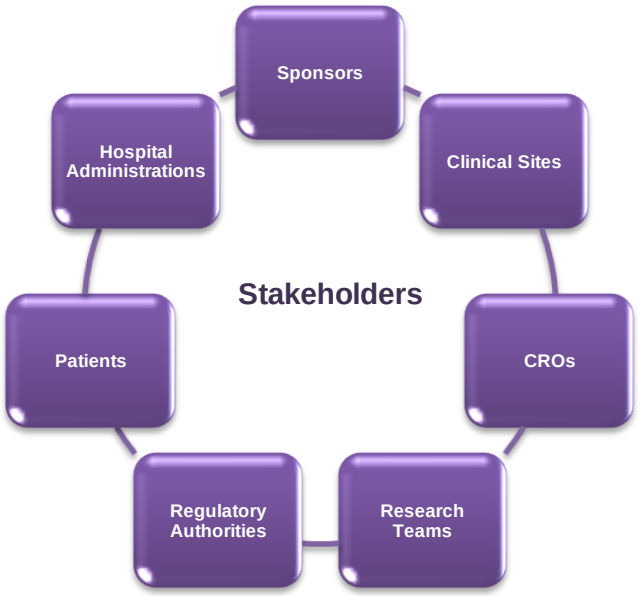

Figure 3. Clinical Trials' Stakeholders (adapted from (10)).

CROs: Clinical Research Organisations

Sponsors are generally pharmaceutical companies or academic institutions that are responsible for the conception, performance, and management or funding of clinical trials. Sometimes, these activities are subcontracted to Clinical Research Organisations (CROs) (7, 10).

Clinical sites are healthcare organisations (public or private funding), laboratories or other entities that gather the needed conditions (technical and human resources) to perform clinical trials. Nowadays, hospitals comprise the majority of the clinical trial sites and in this way, hospital administrations are also considered to be an important stakeholder in what concerns clinical trials (7, 10). Nevertheless, other clinical trial sites begin also to be recognised.

CROs may have several roles in clinical research since they may ensure all research activities or only a few ones (depending upon the scope of their individual work). There are several CROs around the world. Some of them are specialized in some areas of clinical research as clinical monitoring, data management, regulatory activities, pharmacovigilance, etc.

The clinical team is led by a principal investigator (usually a physician) who is responsible for the clinical trial at the site and clinical team coordination. This clinical team may include several figures since sub-investigators, study nurses, pharmacists, study coordinators,

etc. (7, 10). Each one of them has a specific role among the clinical trial which is specified in the protocol and assigned in the delegation log.

Clinical trials may vary in size, and consequently can involve only a single research entity in one country, or multiple entities in multiple countries.

Regulatory Authorities are all those which regulate the pharmaceutical sector (10). Food and Drug Administration (FDA) and European Medicines Agency (EMA) are examples of regulatory authorities. In each country Local Authorities such as Infarmed (*Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.* – National Authority of Medicines and Health Products, in Engli), Ethics Committees as CEIC (*Comissão de Ética para a Investigação Clínica* – Ethics Committee for Clinical Research) and CES (*Comissão de Ética para a Saúde* – Ethics Committee for Health) and CNPD (*Comissão Nacional de Proteção de Dados* – National Committee for Data Protection) for Portugal have an important role in the country's Clinical Research environment.

Patients are the central stakeholder in this scenario since they are the reason for clinical development. Depending on product type and development stage, investigators enrol volunteers first (Phase I), then patients into small pilot studies, and subsequently conduct progressively larger scale comparative studies. As positive safety and efficacy data are gathered, the number of patients typically increases.

All these stakeholders interact with each other in several ways. For instance, regulatory authorities assess the clinical trial application (CTA), as well as supervise its implementation and conduction. Sponsors contract a CRO to conduct, total or partially, the clinical trials. The clinical sites, sponsors and CROs contract investigators, and other technical and administrative staff. The research team identify and enrol patients that fulfil the criteria and accept to participate in the study (10).

All these interactions generate tax revenues to the Government (direct and indirectly). Moreover, additional revenues are generated from the development of new medicines (10).

2.3. Clinical Trials Classification

Clinical trials may be classified according to its purpose. The United States National Institutes of Health organises clinical trials into the following different types:

- Prevention trials – to look for better ways to prevent disease in people who have never had the disease, or to prevent a disease from returning. These may include medicines, vitamins, vaccines, minerals, or lifestyle changes.
- Screening trials – to test the best way to detect certain diseases or health conditions.

- Diagnostic trials – to find better tests or procedures for diagnosing a particular disease or condition.
- Treatment trials – to test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.
- Quality of life trials – to explore ways to improve comfort and quality of life of individuals with chronic diseases. These are supportive care trials.
- Compassionate use trials – to provide partially tested, unapproved therapeutics to a small number of patients who have no other realistic options. Usually, this involves a disease for which no effective therapy has been approved yet, or a patient who has already failed all standard treatments and whose health is too compromised to qualify for participation in randomised clinical trials. Usually, case-by-case approval must be granted by both the FDA and the pharmaceutical company for such exceptions.

Other clinical trials' classification is related to whether the trial design allows changes based on data accumulated during the trial:

- Fixed trials consider existing data only during trial's design. In these kind of trials, they are not modified after beginning and do not assess the results until the study is complete.
- Adaptive clinical trials use existing data to design the trial, and then use interim results to modify the trial as it proceeds. Modifications include dosage, sample size, drug undergoing trial, patient selection criteria and "cocktail" mix. Adaptive trials often employ a Bayesian experimental design to assess trial's progress. In some cases, trials have become an ongoing process that regularly adds and drops therapies and patient groups as more information is gained. The aim is to sooner identify drugs that have a therapeutic effect and patient populations for whom the drug is appropriate.

2.4. Clinical Trials Phases

Clinical drug development involving new drugs are commonly classified into four phases. The drug development process will normally proceed through all four phases over several years. As said before, in a classic approach, the results from each phase determine the design of the next. The successful surpass through these phases will usually lead to the approval by the regulatory authority of a Marketing Authorisation (MA) of a new medicine (7).

Table 1 shows a classification of clinical trials by type and purpose (9, 7).

Table 1. A classification of clinical trials by type and purpose (adapted from (7)).

Phase	Trial Type	Trial Purpose	Examples
I	**Human pharmacology**	Assess tolerability	Dose tolerability trials
		Define PK and PD	Single and multiple dose PK and/or PD trials – some in special patient groups
		Explore drug metabolism and drug interactions	Drug-drug interaction trials
		Estimate activity	
II	**Therapeutic exploratory**	Explore use for the targeted indication	Earliest trials of short duration in narrowly defined, subject populations, using biomarkers or surrogate endpoints
		Estimate dosage for subsequent trials	Dose-response exploration trials
		Provide basis for confirmatory trial design, endpoints and methods	
III	**Therapeutic Confirmatory**	Demonstrate/confirm efficacy	Large, controlled trials to establish efficacy
		Establish safety profile	Randomised parallel dose-response trials
		Provide an adequate basis for assessing the benefit: risk relationship to support licensing	Clinical safety trials
		Establish dose-response relationship	Trials of mortality/morbidity outcomes
			Large simple trials
			Comparative trials
IV	**Therapeutic use**	Refine understanding of benefit-risk relationship in general or special populations and/or environments	Comparative effectiveness trials
		Identify less common adverse reactions	Studies of mortality/morbidity outcomes
		Refine dosing recommendations	Trials of additional endpoints
			Large simple trials
			Pharmacoeconomic studies

PK: Pharmacokinetics *PD: Pharmacodynamics*

Phase I (screening for safety): this “first-in-human” phase intends to answer questions as “Is it bioavailable? Is it tolerated? Does it do anything that might be therapeutically useful?” In this phase, also known as clinical pharmacology, a small number (dozens) of healthy volunteers are subject to trials that intend to assess tolerability, safety, pharmacokinetics and pharmacodynamics – in case a biomarker or surrogate endpoint is available.

Phase II (establishing the efficacy of the drug - usually against placebo): this phase intends to answer the question “Does it seems to work?” It can be subdivided into two subphases: Phase IIa and Phase IIb. Phase IIa trials are about clinical pharmacology in patients with the target disease (small number of patients: 10-200) to assess pharmacodynamics, pharmacokinetics, and dose-response relationships. Phase IIb trials

relate to larger trials in several hundred patients to formally assess the dose-response relationship and increase understanding of efficacy, safety and tolerability.

Phase III (final confirmation of safety and efficacy): these trials intend to answer the question “How well does it work?”. In this phase there are formal randomised controlled therapeutic trials (in hundreds or thousands of patients) to test efficacy and safety of two or more dose levels, and to compare new drug with existing ones. Usually this phase involves a multicentre international programme.

Phase IV (studies during sales): this phase is about to “Look how well it works”. These are post-licensing studies in the target population, with wide entry criteria, to broaden experience in clinical practice. The objectives of this phase are typically surveillance for safety, or further comparisons with other therapy. The results are more likely to be used for marketing purposes than in support of applications to regulatory authorities.

As can be noted, each phase has a different purpose and helps the investigator to answer different questions. However, in addition, it should be noted that before the conduction of clinical trials, pharmaceutical companies conduct extensive preclinical studies (also known as non-clinical studies) as described in Figure 4.

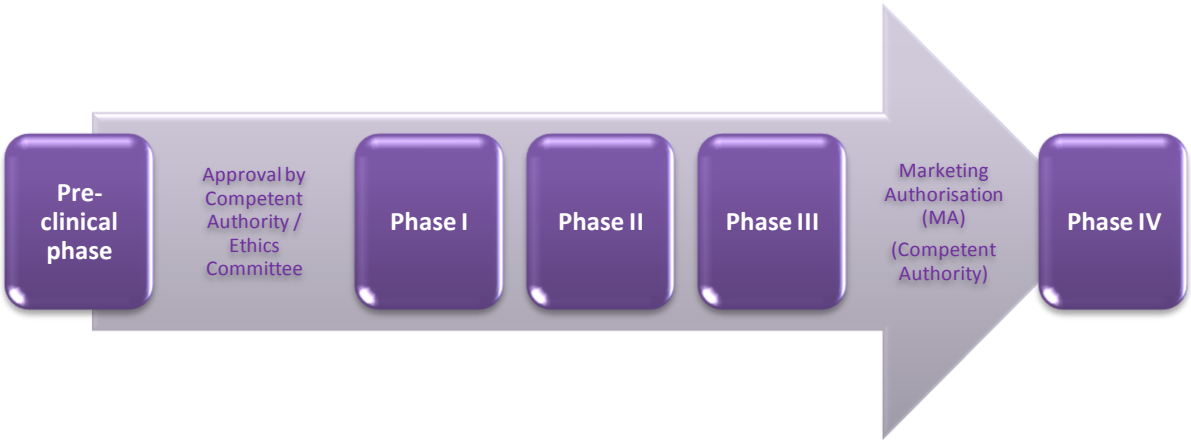

Figure 4. Clinical Trials’ phases in the development of new medicines (adapted from (10)).

MA: Marketing Authorisation

2.5. Other Types of Clinical Research Studies

Randomised clinical trials are an essential part of drug development, but they do not provide all information needed to know a medicine (7).

Clinical research types’ classification is guided by researcher’s behaviour. In this way, clinical studies include both interventional (or experimental) studies and non-interventional

(or observational) studies. In an observational study, the investigator observes the subjects and measures the desired outcomes and does not actively manage the study. In the other hand, in an interventional study the investigator gives the research subjects a particular medicine or other intervention. A clinical trial is an interventional clinical study. Interventional studies may also include those on medical devices and in which surgical, physical or psychotherapeutic procedures are examined. Usually, investigators compare the treated subjects to subjects who receive no treatment or standard treatment. Subsequently, researchers measure subjects' health changes (5, 7).

In contrast to clinical studies, non-interventional studies are those in the context of which knowledge from the treatment of persons with drugs in accordance with the instructions for use specified in their registration is analyzed using epidemiological methods. The diagnosis, treatment and monitoring may be performed according to a previously specified study protocol or exclusively according to medical practice (5, 7).

In an observational study, investigators assess health outcomes in groups of participants according to a protocol or research plan. Participants may receive interventions, which can include medical products, such as drugs or devices, or procedures as part of their routine medical care, but participants are not assigned to specific interventions by the investigator (as in a clinical trial). For example, investigators may observe a group of older adults to learn more about the effects of different lifestyles on cardiac health.

According to Figure 1 there are several types of clinical research studies beyond clinical trials. All of them give their input and have a great impact in the development of medicines and healthcare knowledge.

2.6. New Drug Development

As said before, clinical trials are only a small part of the required research to develop a new treatment. First, there are several laboratorial tests, from discovering, purifying, characterizing and test (in cell and animals). These types of tests are required before conducting clinical trials. In fact, about 1000 potential drugs are tested just before the point of being tested in clinical trials is reached (7).

Nevertheless, the time taken to complete clinical trials continues to be the major holdup in drug development. On average, about eight years pass from the time a medicine enters into clinical trials until it receives approval from regulatory authorities for marketing (7, 10).

Figure 5 demonstrates the cumulative approvals for medicines by FDA in the period 1990 – 2011. New medicines include New Drug Applications (NDAs) and Biologics License Applications (BLAs) (11).

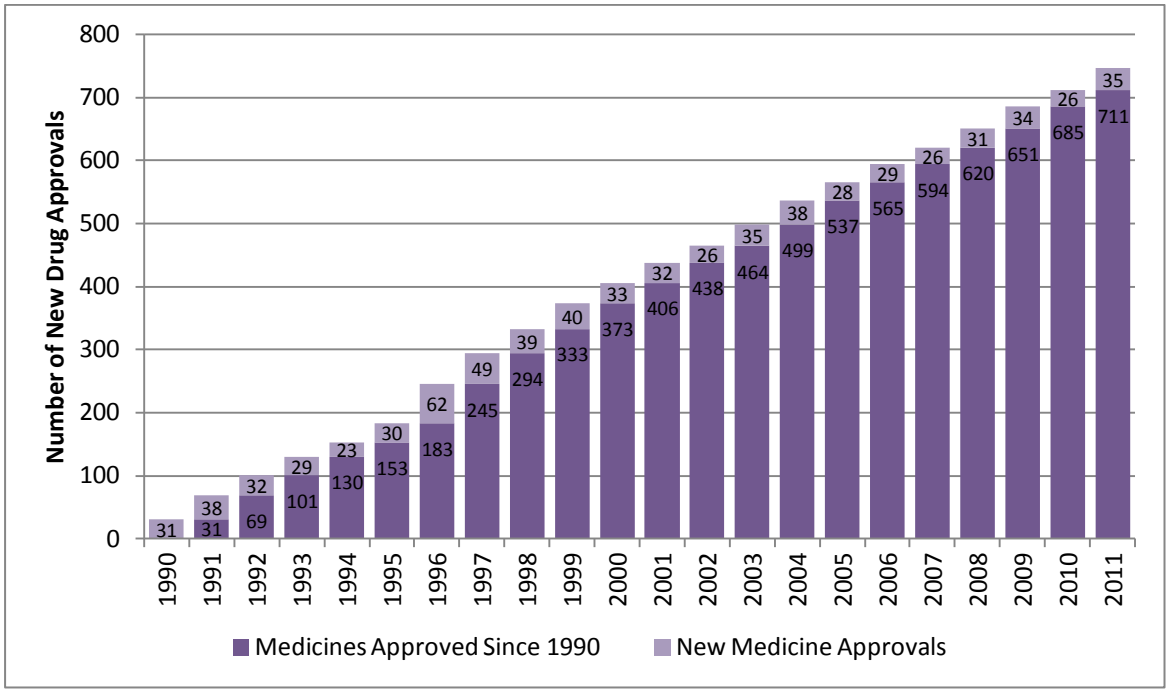

Figure 5. Cumulative Approvals for Medicines in USA (1990-2011) (adapted from (11)).

There are several reasons that lead a clinical trial to last several years. First of all, only certain people who have the target disease condition are eligible to take part of a specific clinical trial. On the other hand, researchers who treat these particular patients must participate in the trial. Then they shall identify the desirable patients and obtain consent from them to take part in the trial.

In certain cases, clinical trials not involving a new drug might have, a much shorter duration. Nevertheless, epidemiological studies are exceptions for this situation.

Nowadays, the level of activity in the pharmaceutical industry's pipeline implies new challenges. Clinical trials are requiring more and more data (which often means more patients) which obviously means more resources. Moreover, real world data is recognised to have much more importance nowadays. This field could also be improved with the conduction of other clinical studies besides clinical trials.

3. CLINICAL RESEARCH IN THE CONTEXT OF COMMUNITY PHARMACY

3.1. PHARMACISTS: SCOPE OF WORK

Pharmacists have competencies to work in various fields, including community pharmacies, hospitals, pharmaceutical industry (development, manufacturing, quality control, marketing and regulatory affairs), medicines' wholesale distribution, clinical analysis and various other analytical activities (chemical, hydrological, microbiological, toxicological, etc.), teaching and research. To practice pharmacy, in Portugal, generally, a pharmacist must register to the Portuguese Pharmaceutical Society, known as "*Ordem dos Farmacêuticos*" (OF). Although not applicable to all pharmaceutical activity areas, this is a mandatory requirement to work in community pharmacy.

Pharmacists' mission is to improve public health by ensuring safe, effective, and appropriate use of medications (12). Many pharmacists, however, felt unsatisfied with their predominant dispensing role and thought that a closer work with patients would make their work more interesting (2). So, over time they have already become more in contact with patients by measuring blood pressure, serum cholesterol and glucose concentration (13, 14). Contemporary pharmacy practice reflects an evolving paradigm from one in which the pharmacist primarily supervises medication distribution and advises patients, to a more expanded and team-based clinical role providing patient-centred medication therapy management, health improvement, and disease prevention services (12, 14). Nowadays, trained pharmacists should be able to develop new skills (13, 14).

Nowadays, pharmacists have extended roles in the community. They have moving from prescription provider to pharmaceutical care provider (1, 3, 15-17, 14). Nevertheless, pharmacists continue arguing for increased scope of practice (1, 18). Pharmacists' professional role expansion has been based on the assumption that they have key roles to play within the healthcare system. However, there are relatively few studies to support this assumption (19, 3). The "Practice of Pharmacy" means interpretation, evaluation, and implementation of medical orders; participation in drug regimen review; drug or drug-related research; patient counselling and all those acts or services necessary to provide pharmacist care in all areas of patient care, including primary care and collaborative pharmacy practice; and the responsibility for compounding and labelling of drugs and devices, proper and safe storage of drugs and devices and maintenance of required records. Pharmacy practice also includes continually optimizing patient safety and quality of services through effective use of emerging technologies (12).

Community pharmacies are considered to be the first point of contact in the healthcare system since they are integrated in community and easy accessed by the population (15, 20). Community pharmacies are the most easy and common way of contact that patients

have with primary healthcare services (20). In this way, today, pharmacists offer a range of services to the community, such as patient education and counselling, medication and lifestyle management, health promotion, screening, prevention and management of chronic diseases (21, 22, 3, 23).

In New Zealand, all pharmacies inquired by Tordoff *et al.* provide some baseline services (advice, dispensing of prescriptions, medicines disposal) and 90% provide home delivery of medicines. 35% of the enquired pharmacists provide screening (e.g. cholesterol, blood pressure), and 32% provide medicines education to community groups (23).

In Portugal, the establishment of pharmacies is determined by demographic and geographic criteria. In 2010, there was one pharmacy for every 3725 citizens. This prevents pharmacies from being concentrated in central urban areas and promotes a more homogeneous distribution throughout the country. Portuguese pharmacies are usually small companies, with an average of 5.7 employees (24, 15). Portuguese pharmacies and their pharmacists actively promote healthy lifestyles and prevention of illness, which makes Portuguese pharmacies a place for healthcare and promoting community's well-being. In fact, the pharmacist plays an active role in promoting the rational use of medicines, pharmacovigilance, health education, disease detection, and in providing medication related information. Besides the regular dispensing role, Portuguese community pharmacists are involved in disease management programmes for diabetes, hypertension and asthma (15). Table 2 shows the ranking of the services provided in the Portuguese community pharmacies (25).

Table 2. Ranking of Pharmaceutical Services (Associação Nacional das Farmácias (ANF) - 2010) (adapted from (25)).

Ranking of Pharmaceutical Services	
1	*Checksaude* – Total Cholesterol
2	*Checksaude* – Blood Pressure
3	*Checksaude* – Glycaemia
4	*Checksaude* – Triglycerides
5	*Checksaude* – Weight
6	Drugs Administration – Miscellaneous
7	*Checksaude* – Pregnancy
8	Diagnostic and Therapeutic aids – Nutrition and Dietetics
9	*Checksaude* – BMI + Waist Circumference
10	*Checksaude* – Uric Acid
11	*Checksaude* – BMI
12	Drugs Administration – Vaccines
13	*Checksaude* – HDL Cholesterol
14	*Checksaude* – Lipid Profile
15	*Checksaude* – Haemoglobin
16	*Checksaude* – PSA

17	Diagnostic and Therapeutic aids – Podology
18	*Checksaude* – FVC
19	*Checksaude* – INR
20	Pharmaceutical Care Program – Diabetes

BMI: Body Mass Index
HDL: High-Density lipoprotein
PSA: Prostate-Specific Antigen
FVC: Force Vital Capacity
INR: International Normalized Ratio

3.2. Pharmacists' Role in Clinical Research

The increasing number of clinical trials worldwide has opened a range of new opportunities for those wishing to work in the clinical research field. The design, coordination and analysis of a clinical trial require a multidisciplinary team: principal and sub-investigators, clinical research coordinators (CRC), research pharmacists, clinical research associates (CRA), and many others (26).

Pharmacists can play an important role in the way clinical trials are conducted and may contribute in several ways in the research process. They can use their expertise and collaborate directly on pharmaceutical issues such as drug composition and management of indications, dosage, administration, contraindications, adverse effects and interactions of the investigational medicinal product (IMP). Pharmacists can also help to ensure the safety of human subjects and the protection of their rights. For instance this can be done through the participation in local Institutional Review Boards (IRBs) or Independent Ethics Committees (IECs) (26).

The accurate control and management of an IMP is an important issue to the success of a clinical study. Pharmacist, as the drug specialist, is the most suitable team member for this task (26).

Pharmacist role in clinical studies includes ensuring that the drug receipt is recorded in the study documents or in the interactive voice (or web) response system (IVRS/IWRS). Pharmacist has also the primary responsibility of drug dispensing. They should only dispense an adequate amount of IMP to each subject and this amount should cover dose requirements until the next visit. It is important that patients are aware of the need to return all unused medication. It is pharmacists' duty to verify the medicinal product packaging and labelling, the drug substance analysis, pharmaceutical form, batch number, manufacturing and expiration dates, the correct use, handling and storage conditions (temperature, light and humidity), the drug administration routes and specific dosage. Pharmacists should also be aware of all dispensing, incinerating and handling procedures in case of chemotherapy drugs. In the end of the day, pharmacists should ensure that the IMP is in good condition for use. All the conditions described above are determined and stated by the sponsor and all data should be completely recorded (26).

During IMP's receipt and shipment, the pharmacist should ensure that the transportation is performed according to the instructions specified by the sponsor. If there are any questions regarding the quality or physical aspects of the IMP, the pharmacist should not

distribute the drug and must immediately contact the sponsor (26, 27). Given the above, pharmacists must be familiar with the clinical trial protocol (CTP), informed consent form (ICF), investigator's brochure (IB), and standard operational procedures (SOPs) of the research site, which include regulatory, ethical, and legal requirements.

Instead of working specifically as a pharmacist in research projects, pharmacists may rather work as CRC (Clinical Research Coordinator). The CRC's role is assisting the investigator to comply with the research project requirements, aiming to obtain reliable trial results and to ensure the well-being of subjects involved in the study (26, 28, 29).

Data quality is required to guarantee that study data is reliable and complete in order to accurately assess the safety and effectiveness of medicinal products. The accuracy of data entry is verified by a CRA (Clinical Research Associate) who is also responsible for evaluating whether the clinical study is being conducted according to the ICH GCP and applicable requirements. All clinical studies require continuous data and safety monitoring, which is sent to the sponsor. The monitoring visits enable the CRA to act as a link between the sponsor and the research site. Pharmacists have competencies that enable them to perform this role perfectly (26).

At this time, pharmacists are at the forefront of patient care and have a significant impact on patients' management. Moreover, the pharmacist may play a central role in the research process, which can influence directly the success of a clinical trial (26). To participate in clinical research, pharmacists would also need adequate facilities, a strong professional motivation and a good relationship with the public and local physicians (13).

There are few pharmacists practicing in institutional settings and most people who benefit from pharmacy services are in the community. Thus, evidence of the impact of pharmacists' interventions in community settings must be generated (19). Moreover, most pharmacists in community practice have had limited exposure to clinical research methodology (19). Academic researchers' skills may lead them to design rigorous experimental studies, but taking that research to the field requires active participation of pharmacy professionals.

3.3. Practice-Based Research

The concept of using community pharmacies for practice-based research is relatively new. Little is known about community pharmacists' willingness to participate in community-based research and the perceived barriers to participation (30). Figure 6 intends to illustrate the importance of practice-based research for translating research into practice and into materials for patients (31, 32).

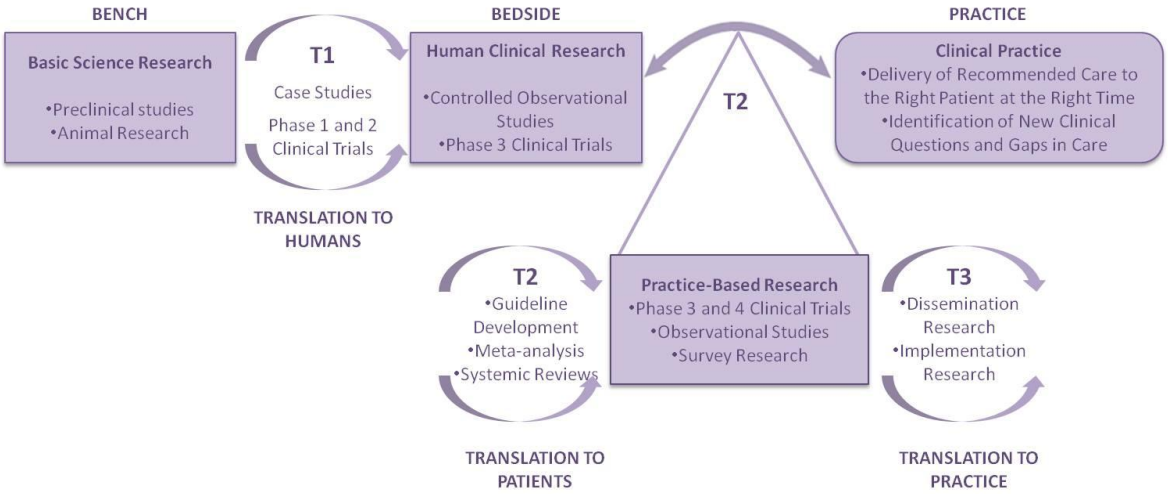

Figure 6. The importance of practice-based research for translating research into practice (adapted from (31)).

Kosta *et al.*, aim to explore how pharmacists involved in the Pharmacy Study Of Natural Health Product Adverse Reactions (SONAR) project perceived the barriers and facilitators to participate in clinical research (33). Also Peterson *et al.* aim to conduct an Australian national cross-sectional survey of randomly selected Australian pharmacists to determine their attitudes towards the involvement in pharmacy practice research. Survey questions assessed attitudes to research, involvement in research, barriers and facilitators to involvement, self-assessed understanding of research terminology, and access to and use of electronic bibliographic databases (34).

Previous studies of pharmacy-based clinical research participation focused on estimating how many pharmacists were willing to participate in research without attempting to fully understand why (33). Three studies in the United Kingdom reported that the percentage of pharmacists willing to participate in research varies from 32 to 48% but only 6% of the surveyed pharmacists had ever participated in research (35-38). The study from Australia reported that pharmacists previously involved in research would much more readily consider future research participation (77%) than pharmacists who had never participated in research (34%) (38), (39). A Canadian study showed that pharmacists participate in research motivated by a general interest in clinical research, believing that participation will lead to better disease management and perceived patient benefits (19). The Australian survey quoted above mentions that approximately one-third of the responding pharmacists are nowadays, or had been in the past, involved in research activities, and generally reported positive experiences (34).

Lack of time or experience and training in research appear as the main barriers to pharmacists' participation in research (19, 35-37, 39, 34, 33, 40). This applies not only to pharmacists as well as doctors and nurses (41, 40, 42). Other barriers identified were: lack of monetary reward and/or fear that participation would lead to losing money; staffing challenges and fear that participation would draw the staff away from their primary assignments; communication problems between researchers and pharmacists; the

pharmacy mindset which has been described as a feeling of skills absence or knowledge and/or the need of a belief that participating in study would yield useful results; (38).

The factors that encourage pharmacists to participate in research are (34):

- desire to improve the career;
- opportunity to learn more about disease management;
- opportunity to provide enhanced services to patients;
- personal interest.

To overcome barriers to pharmacists' participation in research strategies are proposed, such as having students conducting research in pharmacies, pharmacy research awareness programmes and encouraging and providing training to pharmacy staff members (38). Placing students in pharmacies to participate in research studies seems a good way to change their mindset in favour of research participation (33). However, neither this or the preceding strategies have been adequately tested, nor have any of the prior studies explained why some pharmacists participate in research despite all the identified barriers, while others find the barriers impassable (33).

Understanding perceptions of time or lack of it appears to be a key to understand why healthcare professionals in general, and pharmacists in particular, find research participation challenging. In fact, the concept of time is shaped by the social context and the point of view of the person measuring it. It cannot be limited to an objective assessment of the number of hours required to complete research-related tasks (33).

The Pharmacy SONAR project was a pilot study conducted from March 2008 to August 2009 in ten community pharmacies in the greater Toronto area, Ontario, Canada, aiming to assess the feasibility of using an active surveillance system in which community pharmacies asked patients, who was picking up prescriptions, about their use of natural health products (NHPs) and possible related adverse events (AEs) (43, 33). A subsequent study explores how involved pharmacists perceived the barriers and facilitators related to participation in clinical research, in an attempt to understand pharmacy staff members' experiences of participating in a pharmacy-based research study (33).

The most important challenges related to participation in the SONAR study identified by the participants were (a) lack of time; (b) difficulty to remember asking the study questions; (c) perceived lack of knowledge about NHPs, and (d) communication difficulties (33):

(a) **Time -** Time was identified as the biggest challenge to both participation in the study and good performance in the study. Although acknowledging that the three questions asked took a very short amount of time, the participants reported that the competing demands, on their time, made a few minutes seem difficult.

(b) **Remembering to ask the questions -** It has been found that failing to remember to ask the questions and making this part of a daily work routine was, perhaps, even bigger obstacle for study participants.

(c) **Perceived lack of NHP-related knowledge -** Another issue found was that many pharmacists were hesitant to ask the probing questions because they were worried that the questions may encourage patients to ask additional information on NHPs. Pharmacy staff members felt inhibited due to their perceived lack of NHP knowledge, despite the NHP references provided and SONAR team support and follow-up.

(d) **Communication difficulties -** Communication difficulties were identified between the study team and the pharmacy staff members and between the various pharmacy staff members themselves. The SONAR research assistant considered challenging to work with pharmacy owners or managers who were willing to allow their pharmacy to participate in the study, but whose pharmacy staff did not know what to expect and had trouble with the data collection itself.

As seen above, this study was able to include pharmacy staff members in a research project and then analyse their perceptions for participation (33). However, given the case-study design and convenience sampling, it is not clear whether the participating pharmacy staff members can be seen as representative of all pharmacy staff members in Canada or elsewhere. It is remarkable that approximately 75% of all pharmacies contacted by the study team turned down the offer to participate, giving just common reasons, where lack of time was the most significant one (33). It seems that some of the participating pharmacists were not comfortable in sharing their true opinion on this study and some have given polite but not truthful answers (33). It could also be noticed that there is some absence of clarity around the protocol, because participants did not give any real importance to data collection, reflecting their perception of the lack of value on research in general. The results of this study suggest that the "forgetting" was related to lack of clarity (33).

On the other hand, although there was overwhelming recognition of clinical research's value to the profession, few pharmacists possessed a good understanding of key terms related to research and evidence-based practice (e.g., *P*-value or number needed to treat) (34).

It should be noted that this mindset about practice-based research should be changed since students enter pharmacy course in university. Kritikos *et al.*, intended to show the undergraduate pharmacy students' perception to research and their attitudes towards pharmacy practice research (PPR) through a 23-item survey (3). It was administered to all students enrolled in the 4th grade of pharmacy undergraduate programme of the University of Sydney (Australia). In total, 853 students responded to the survey leading to 83% response rate. This study showed that while students perceived research to be necessary, they found it difficult and were divided in their interests in follow research. Most students agreed that pharmacy practice research plays an important part in the profession and curriculum but almost half of them lacked confidence to undertake it. The majority didn't show positive attitudes towards the role of PPR in the curriculum, nor engaged in its activities, showed reliability on it, or expressed interest in college's involvement and the role of PPR in the career (3).

This study might be of great importance whether it is intended to change pharmaceutical mindset to practice-based research. It is not just the pharmacists' perception that matter, but also future pharmacists, those who are now at university.

There are two key factors that might explain the relative lack of pharmacy practice-based research: lack of pharmacists' knowledge and experience of research, and lack of understanding of the impact of pharmacists in health system (19, 44).

3.4. COMMUNITY PHARMACY RESEARCH NETWORK (CPRN)

As it was said before, the concept of using community pharmacies for practice-based research is relatively new. Moreover, little is known about community pharmacists' willingness to participate in community-based research and the perceived barriers to participation (30).

To assess the interest of American Pharmacy Services Corporation (APSC) independent community pharmacists to participate in a community pharmacy research network (CPRN) a study was conducted. It showed that in Kentucky the majority of pharmacists (83%) responding to the survey indicated that were "interested" or "very interested" to participate in a community pharmacy research network. Although respondents reported being willing to participate for about 6 hours per week in a CPRN, they pointed time as being the greatest barrier to participation (30).

It should be noted that of 191 surveys sent to pharmacies, only 65 were returned (34%). The demographic information collected (including age, gender, pharmacy degree, and years of community practice) showed that the majority of respondents were males (58.5%) who were independent community pharmacy owners. The pharmacy's data collected (including number of prescriptions dispensed per week, hours of operation, and staff number) also showed that more respondents worked in a rural pharmacy setting (72.3%) than in an urban one (27.7%) (30).

This survey also included questions probing interest in CRPN participation (*cf.* Figure 7) and questions about perceived barriers. More than 42% of the respondents strongly agreed and 34.4% agreed that "community pharmacist play an important role in healthcare-related research", while 21.9% disagreed and only 1.6% strongly disagreed with this statement. Pharmacists agreed that having the opportunity to affect the practice of community pharmacy and improve independent pharmacy services was the most important factor in deciding whether to participate in a CPRN. The opportunity to participate in a study that may be published in a journal and the opportunity to present the results of a research project at a regional or national level seemed to be less important for the study pharmacists. Job satisfaction would slightly increase for 51.6% of the respondents and financial compensation was ranked as the most important factor for participation by 16.4% of the respondents. Moreover 92.1% of the respondents indicated

they were interested in obtaining additional information about opportunities to participate in a CPRN (30).

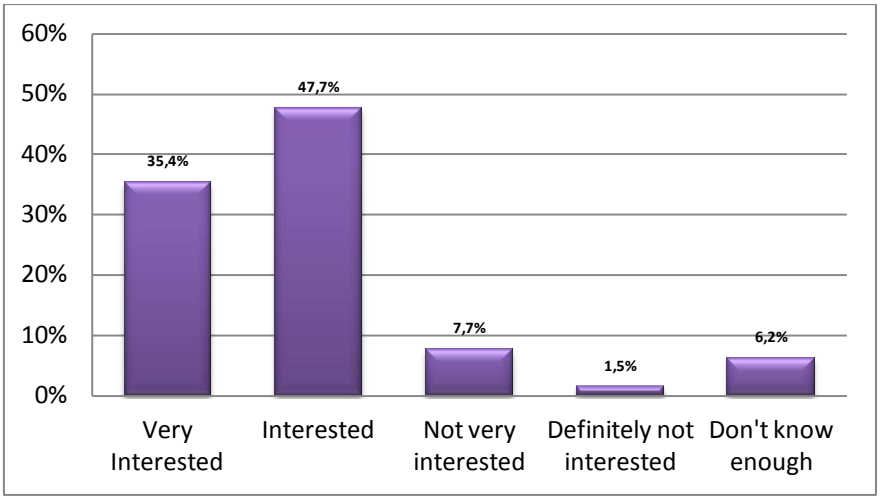

Figure 7. Level of interest in participation in a CPRN of independent community pharmacists (n=65) (adapted from (30)).

This study also focused on the motivators that might influence pharmacists' decision to participate in a CPRN. Figure 8 shows the importance of four motivators provided in this study: research assistant provided by the network; relief pharmacist provided by the network; becoming an advanced pharmacy practice experience (APPE) preceptor; and having the opportunity to suggest a research topic (30).

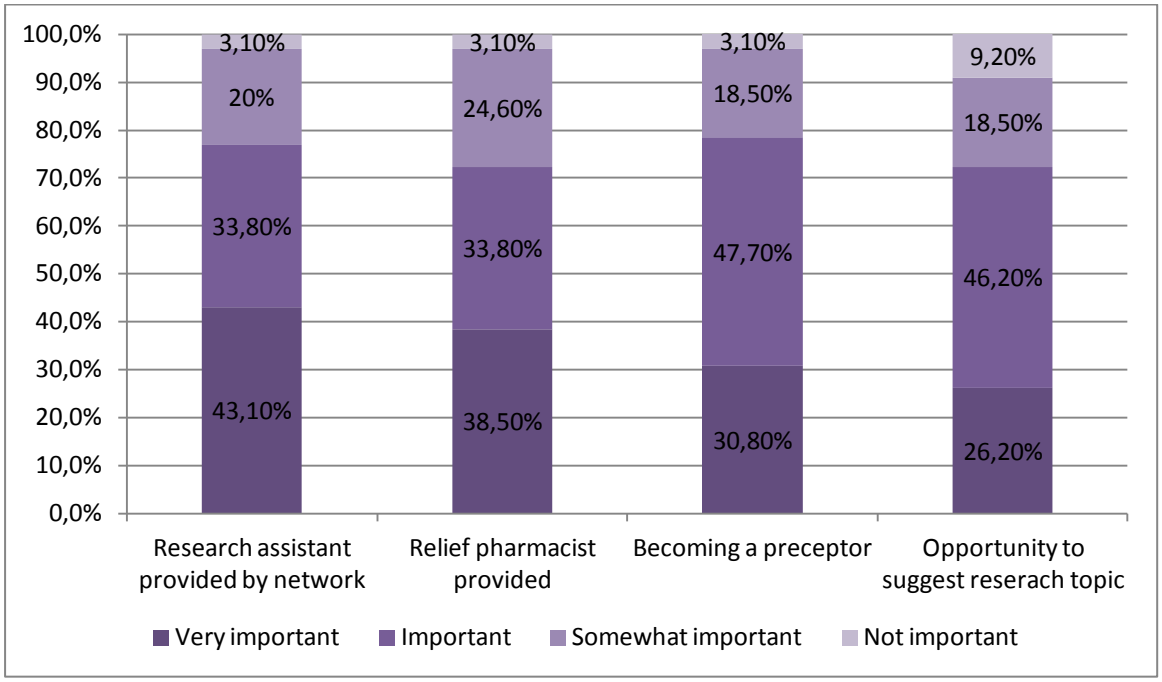

Figure 8. Motivators in decision to participate in a CPRN of independent community pharmacists (n=65) (adapted from (30))

The importance that each pharmacist gives to their participation in a CPRN also varies according to the importance they give to several factors. Figure 9 shows how the importance of various benefits of participating in a CPRN influence pharmacists' decision to participate among four possible options. (30)

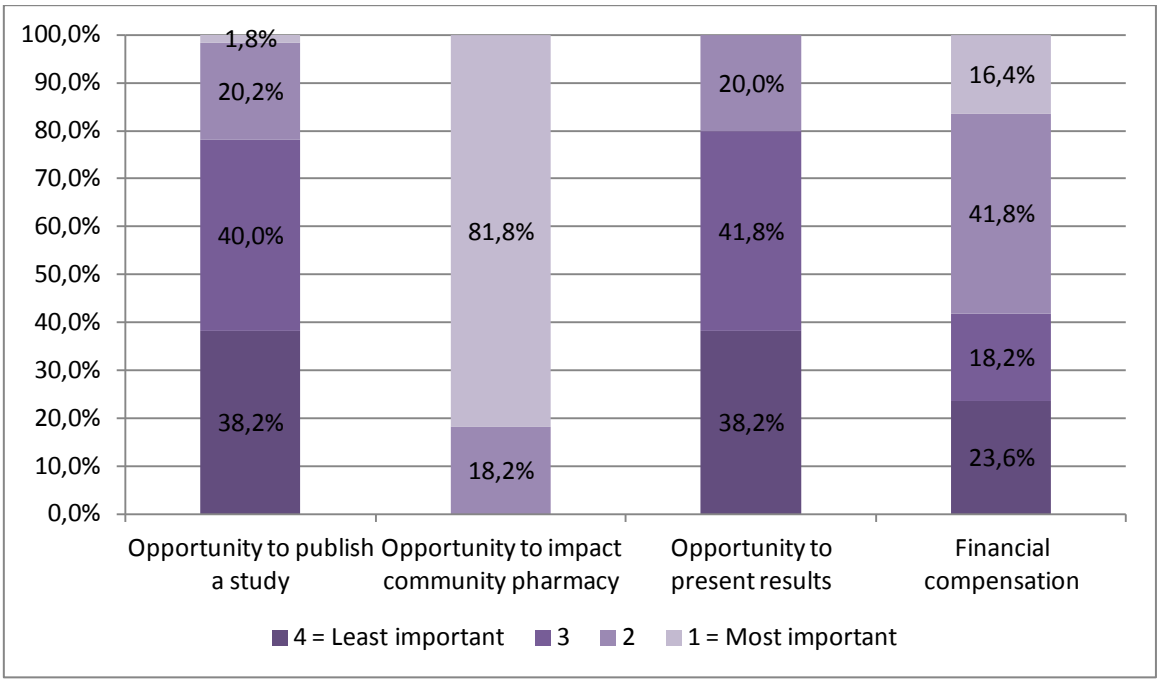

Figure 9. Level of importance in decision to participate in a CPRN of independent community pharmacists (n=65) (adapted from (30)).

CPRNs have the potential to be a valuable tool that pharmacies can use to solve issues related to the practice of pharmacy and improve patient care. However, as this study population consisted of independent community pharmacists who were members of an independent pharmacy cooperative, the results cannot be extrapolated to other practice settings and may not apply to independent pharmacists who are not members of a cooperative, whereby additional research is needed to capture the interest of pharmacists practicing in other settings (30).

3.5. The role of Community Pharmacists in Clinical Trials

The primary objective of researchers of health services (including community pharmacies) in the conduction of randomised controlled trials (RCT) is to evaluate interventions to improve the organization, delivery, quality, and/or outcomes of care. The application of

these trials in academic or other settings allow a reasonable degree of control over key factors essential to conduct a well designed RCT. This enhances the internal validity of a study but may turn it less generalizable to non-academic settings (44). Weinberger *et al.* faced this issue on their study about the particular case of community pharmacies. They tried to describe unexpected challenges and possible strategies, when conducting randomised controlled trials of health services research interventions, in community pharmacies (44).

With this purpose, they conducted an RCT to evaluate the effectiveness of an intervention to increase pharmacists' involvement in caring for customers. They concluded that health services researchers should conduct RCTs in a variety of non-academic practice settings to increase generalizability and better reflect the true impact of interventions. Pragmatic problems, although significant, can be successfully overcome. The authors offer other investigators some advice, based on their experience: to conduct researches that are consistent with corporate goals; to involve the appropriate corporate persons early in the process and to be flexible. Summing up, the authors referred that conducting RCTs in a variety of practice settings should continue to be a goal for health services researchers (44).

As it was said before, pharmacists are already becoming more "hands on" by measuring blood pressure or serum concentration. To participate in clinical research, pharmacists need adequate facilities, a good relationship with the public and general physicians, and strong professional motivation. Training would allow them to develop new skills (13).

3.5.1. RECRUITMENT

The conduction of clinical trials has a determinant step concerning recruitment. Timely patient recruitment is widely acknowledged to be the single most important aspect for the success of a clinical trial ever since the recruitment process is often extensive, difficult and expensive. The restricted inclusion and exclusion criteria, the increased number of patient visits and a growing demand for participation from diverse populations, made trial protocols becoming much more complex hindering the recruitment process. All this implications lead to delays, which will extend the time to market for new drugs and could have additional costs to the sponsor (45, 46).

There is a need to patients to be more aware of clinical trials and its participation benefits and opportunities. The source of information needs to be trustable so the patient can be confident that the participation is a good decision (45). The proximity patient-pharmacist that has showed so many benefits in so many distinct areas has also a useful impact. The decision to participate in a clinical trial is greatly affected by social, psychological and emotional factors (45).

The participation of pharmacies in the recruitment process is not new. In fact, since the mid-1990s pharmacies have been used for patient recruitment. Nevertheless, the early programs only involved the notification of a pharmacy's patients by letter that they might

be eligible for a nearby clinical trial (45). Nowadays the more common way to a patient be aware of a clinical trial is through the clinical trial sites and investigators, but their capacity to meet increasing demand for more patients and more diverse patient populations seems insufficient (45).

The community pharmacy has gained an increasing important role on patients' daily life, since patients visit their local pharmacies for basic healthcare needs. Moreover, the general public and pharmacists want the profession to be more proactive in disseminating information about clinical trials (45).

Corelli *et al*. held a study that enhances the above said importance of pharmacies in the recruitment process. Study sites were 64 community pharmacies in Connecticut (n=32) and Washington (n=32) which due to their geographically disparate locations, gave rural, suburban and urban settings to the study (47).

This recruitment process began with the identification of pharmacies. To identify potential participating pharmacies it was obtained a complete and current listing of licensed pharmacies.

The process to determine interest in participation and confirm inclusion/exclusion criteria occurred over a period of time whereby the pharmacy contact was presented with the information and given time to consider participation and discuss with their staff (pharmacists and pharmacy technicians). Figure 10 (adapted from Corelli *et al.*) shows the recruitment and enrolment of participating pharmacies (47).

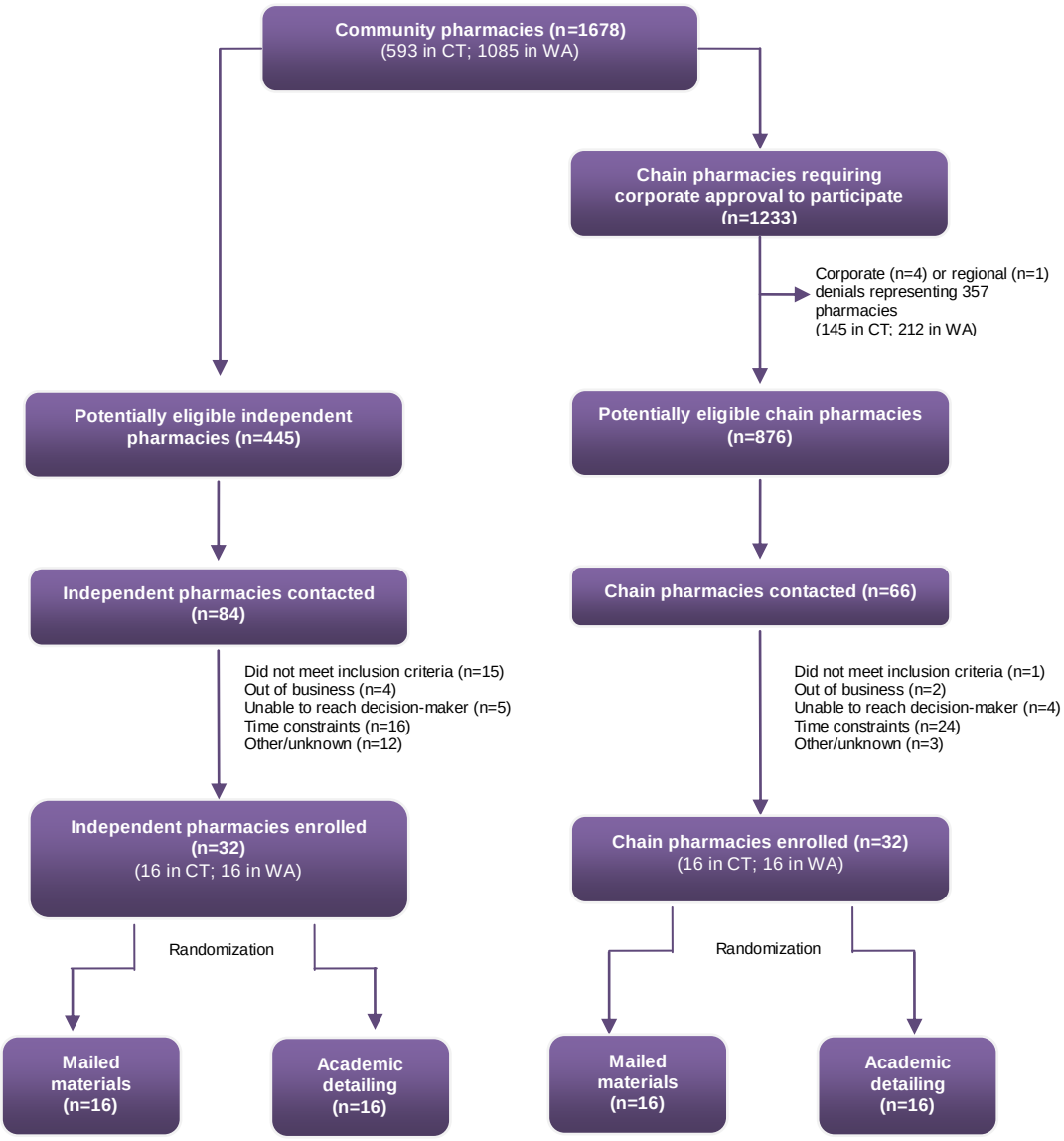

Figure 10. Recruitment and enrollment of participating pharmacies (adapted from (47)).

CT: Connecticut *WA: Washington*

The study of Corelli *et al.* reveal that recruitment and consent of pharmacy personnel was a labour-intensive and time-consuming process requiring a median of 5 contacts over a median of 25 days (47). Efforts need to be implemented in community pharmacy participation in translational research. This would demonstrate the value of pharmacy services in health care system. It is important to engage pharmacy personnel to participate in “real-world” community settings in order to change small number of published studies within pharmacy-based research (47).

3.5.2. EDUCATION ABOUT CLINICAL TRIALS

A 19 item public survey gathered on April 2010 (2650 people in 50 states and wide range of ages, health conditions, education levels, clinical trial knowledge, and pharmacy type used) tried to answer if pharmacists are a viable channel for education about clinical trial participation. It has been showed that 80% of respondents want their pharmacist to tell them about clinical trials. Nevertheless, 98% never asked a pharmacist for information about trials since the information given by their pharmacist is only 1% related to clinical trials (48, 49).

In general, pharmacists give patients information about (48, 49):

- the medicine (a printout on use/side effects) – 85%
- the medicine (talks about use/side effects) – 40%
- medicine that can be bought without a prescription – 24%
- insurance – 21%
- other treatments – 6%
- doctors or hospitals – 3%
- other information – 3%
- clinical trials – 1%

Surveyed people also refer they would like to receive information about trials from a pharmacist by printed information at the pharmacy (69%); email (49%); talking to a pharmacist at the pharmacy (40%); mail (21%); telephone (7%) or other (3%) (48, 49).

56% of the surveyed patients would want to ask a pharmacist about how they can find a trial for themselves, a friend or family and 45% would ask if clinical trials are safe. Moreover, 44% would ask how they would learn more about trials, 32% wonder how do clinical trials work and 18% would question what is a clinical trial and 12% why are clinical trials needed (48, 49).

On the other hand, a online pharmacists' survey in 50 states gathered 213 respondents: 69 community independent pharmacists, 62 hospital/institutional pharmacists and 82 pharmacists in other settings. A mix of managers and front-line pharmacists who interact with patients revealed that they think it is very important to educate pharmacy patients/customers about clinical trial participation before they enrol (87%) (48, 49).

The inquired pharmacists demonstrated they were somewhat willing (34%) or very willing (56%) to provide trial information if they knew that patients/customers were interested in receiving trial information. Pharmacists think the most effective means of providing information are conversation with patients/customers (75%), by a general education brochure (75%), by an automatically-generated list of appropriate trials (64%), an information kiosk (63%), conducting seminars (59%), an opt-in service to automatically receive information (54%) or showing a video (32%) (48, 49).

Figure 11 shows the topics which pharmacists feel prepared to discuss with a patient/customer (48, 49).

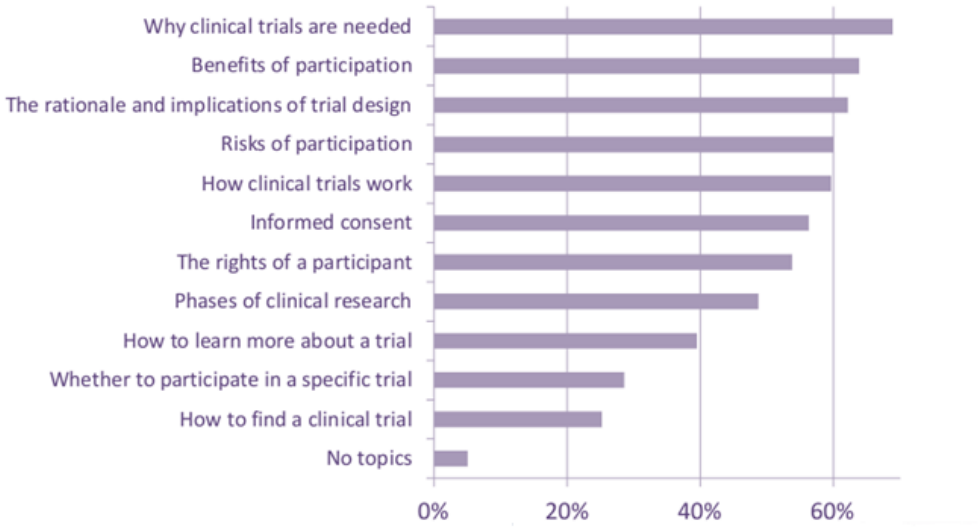

Figure 11. Topics which pharmacists feel prepared to discuss with a patient/customer (adapted from (48, 49)).

As it was said before, the lack of public awareness and understanding about clinical research has long hindered the efficiency and speed in recruiting patients to participate in clinical trials. It was found that only 1 in 3 adults had even heard of clinical trials (50, 45, 51). The Center for Information and Study on Clinical Research Participation (CISCRP) showed that pharmacists might be a viable channel to educate and engage the public about clinical research, and the results suggested that pharmacy-directed outreach and education are feasible .

Another study was conducted to verify the impact of in-pharmacy education on patient comprehension and willingness to participate in clinical research. In collaboration with McKesson and its network of independent community pharmacies, CISCRP trained 32 pharmacists and provided them with educational materials to display and/or distribute at their pharmacies for a period of 2 to 3 months. Pre-surveys and post-surveys among 487 patients were conducted to gather baseline measures and to assess the impact of educational materials and in-pharmacy discussions. A post-survey was also conducted among pharmacists. The results of the study showed that patient discussions with their pharmacists and revision of educational materials distributed through pharmacies positively impacted patient awareness, comprehension, and willingness to participate in clinical trials. Indeed, during the study period, 4% of patients who reviewed the materials chose to volunteer for clinical trials. Nearly all baseline measures of awareness and comprehension increased 10 to 20%. Respondents were more interested in learning about clinical research after speaking with their pharmacists and reviewing educational materials, and 40% were more likely to recommend participation to a friend or family member (48, 49).

4. CLINICAL RESEARCH IN A COMMUNITY PHARMACY SETTING – REAL-LIFE EXAMPLES

The conduction of Clinical Research in the context of Community Pharmacies is already a reality. Several approaches may be use to bring Community Pharmacies into Clinical Research.

4.1. RANDOMISED CLINICAL TRIALS ON STUDY DRUGS

4.1.1. COMMUNITY PHARMACISTS AS LOCAL INVESTIGATORS IN A CLINICAL TRIAL: THE SINUTAB® STUDY

A new formula of Sinutab® (Paracetamol 500 mg and Pseudoephedrine 30 mg) was approved for registration in Belgium. The registration was conditional since the regulatory authorities requested a clinical trial in order to prove the efficacy of the fixed combination. To meet this objective, a clinical trial was conducted in Belgian community pharmacies (52).

The main objectives of the study of Laekeman *et al*. were the presentation of the clinical results of the trial and a reflection on the experience of conducting trials in a community pharmacy setting (52).

It was a randomised, double blind, placebo-controlled, comparative phase 4 multicentre study in parallel between Sinutab® and placebo. Individuals were included if they were older than 18 years but excluded if they were using any medication possibly interfering with the study drug. In order to fulfil this requirement the medication history of all patients was available in the pharmacy's computer (52).

Aiming a target of 300 evaluable subjects, 451 subjects were included (mean age 38 years). The treatment was established as follow: two Sinutab® or placebo tablets three times a day during 5 days (52).

The setting of this study was Belgian community pharmacies with one community pharmacist per pharmacy as local investigator (n=35). The study was approved by University Hospital of Antwerp's Ethics Committee and was externally audited (52).

The main outcome measures of this study were (52):

- Primary: "The effectiveness of Sinutab® on the relief of nasal congestion and headache in subjects with a common cold"

- Secondary: “The effectiveness on the Major Symptom Complex (MSC) of common cold; the number of days lost at work or school; the quality of life during daytime and at night; the time-to-resolution of the common cold; the overall safety of Sinutab®.”

There were some parameters that changed significantly favouring Sinutab® over the treatment period: nasal congestion and headache ($P < 0.001$) (primary outcome); major symptoms complex (MSC) ($P < 0.001$); sore throat ($P < 0.024$); pressure around the eyes ($P < 0.001$); interference with concentration ($P < 0.001$); interference with sleep ($P < 0.066$) (52).

This study also paid attention to the adverse events (AEs). Those occurring more often were fatigue (37), dizziness (27), nausea (27), myalgia (18), sleep disorder (14), dry mouth (14) and upper abdominal pain (13). Apart from the myalgia, more subjects in the Sinutab® group suffered from these AEs than in the Placebo group (52).

This study concluded that the combination of paracetamol with pseudoephedrine in Sinutab® improved significantly all symptoms towards placebo and that no serious adverse events occurred (52).

Since this was the first clinical trial of this dimension with community pharmacists taking clinical responsibility as local investigators, the authors stated that they acquired skills and knowledge which could be used in the future and the knowledge would be spread (52).

4.2. Randomised Clinical Trials on Pharmaceutical intervention programs

4.2.1. Effectiveness of a Community Pharmacist Intervention in Diabetes Care: a Randomised Controlled Trial

To date, European studies on the impact of community pharmacist interventions in Diabetes are scarce. There is little evidence from well designed randomised controlled trials about the impact of community pharmacist’s intervention on the clinical management of patients with type 2 Diabetes (53).

To address this evidence gap, an RCT was initiated in Belgium, in order to study the effectiveness, and sustainability of effects, of a community pharmacist intervention in Diabetes care (53).

Mehuys *et al.* carried out a 6-month, randomised, controlled, parallel-group trial in 66 community pharmacies in Belgium. The pharmacists’ participation in this study was voluntary and the recruitment was made through a call by three professional pharmacist

associations. Each pharmacy was asked to recruit five patients and each participant's physician was informed about the study by letter (53).

This study follows the same rules than other clinical trials in what concerns performance according to Declaration of Helsinki and GCP guidelines. It was approved by Ghent University Hospital's Ethics Committee and it was given written informed consent (53).

In this study, randomisation was made at the pharmacy level: each participating pharmacy was randomly assigned to either the control group or the intervention group. Patients in the control group received usual pharmacy care, while patients in the intervention group received a protocol-defined intervention at the start of the study and at each prescription-refill visit, during the study (53).

The intervention design was based on previous observational data concerning Diabetes management in Belgium (54):

- Education about type 2 Diabetes and its complications;
- Education about the correct use of oral hypoglycaemic agents (timing in relation to food);
- Facilitation of treatment compliance (by counselling);
- Healthy lifestyle education (diet, physical exercise and smoking cessation);
- Reminders about annual eye and feet examinations.

The elements above were implemented by the pharmacist on each visit of the patient during the 6-month intervention period (53).

It should be noticed that before the start of the study, the intervention pharmacists underwent a training session to understand the study protocol and to deepen knowledge on the pathophysiology of type 2 Diabetes and its non-pharmacological and pharmacological management according to current treatment guidelines. The control pharmacists only received training on the study protocol (53).

This study mainly focused on correct medication use, medication adherence and healthy lifestyle promotion. It showed that the community pharmacist intervention significantly reduced HbA1c (between-group difference: 0.5%, P=0.009) (53).

4.2.2. Randomised Controlled Trial Protocol on intervention in Depressed Primary Care

Pharmaceutical Care Program for Pharmacological Treatment of Depression in Primary Care (PRODEFAR) consists of a series of educational interventions focused on improving patients' knowledge of antidepressant medication, as well as making patients aware of the importance of compliance to the medication. The PRODEFAR study intends to evaluate the effectiveness and cost-effectiveness of a community pharmacist intervention developed to improve patients' compliance and outcomes of primary care patients with depression, providing valuable information for health professionals and policy makers.

This trial, held in Barcelona (Spain), compares patients receiving a pharmaceutical care support program in primary care with patients receiving usual care (55).

The importance of including community pharmacists, who are considered the health professional most readily accessible to patients, as active members of multidisciplinary healthcare teams was emphasized by the World Health Organisation (WHO) and the European Council. Community pharmacies have shown improvement in patient wellbeing, in chronic physical conditions (55).

Therefore, this study aims to evaluate the efficacy of a pharmaceutical care program, compared with usual care, on the improvement of adherence to anti-depressant drugs and patient wellbeing in a population with a diagnosis of depression treated in primary care under real practice circumstances (55).

The methodology used on this study was a 6-month follow-up naturalistic randomised controlled trial with random allocation of participants into two alternative branches: usual medical and pharmaceutical care plus support programme in community pharmacy (intervention group) and usual medical and pharmaceutical care (control group), as described in Figure 12 (55).

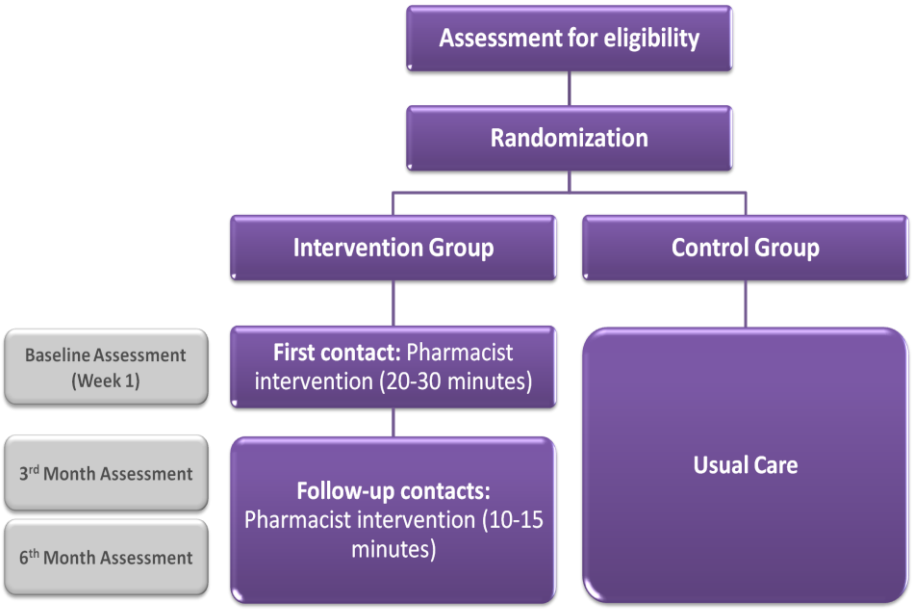

Figure 12. Study Design (adapted from (55)).

Two of the inquired pharmacies (13%) refused to participate in the study due to deep workload and lack of interest in the study. Therefore, 13 pharmacies with a total of 34 pharmacists would be responsible for providing patients with the intervention and usual care during the 6 month follow-up period (55).

Since it was a randomised clinical trial, randomisation was generated at the patient level by a computerized random-number generator with a ratio 1:1. Then, when the patient

went to the pharmacy and gave the prescription to their pharmacist, they opened the envelope and created a patient study chart distinguishing between control and intervention group. The blinding of participants or pharmacists (investigators) is not possible due to the type of intervention (55).

In this study, patients enrolled to the intervention group would receive the support program in community pharmacy (PRODEFAR) every time they went to pharmacy to pick up the prescription or asked advice in the 6-month duration of the study (55).

The participation in this study required the pharmacists to be trained. In this case, pharmacists participating in the study received 8 hours of training about PRODEFAR prior to the study. Obviously, patients in the intervention group were asked to avoid conversations regarding the program with patients of the control group, in order to prevent bias. The measurements of this study were made through assessment visits (at baseline, 3 and 6 months) conducted by independent and blinded interviewers (55).

4.3. Real World Data on Pre-licenses

The Salford Lung Study is the world's first pragmatic Randomised Clinical trial (pRCT) to compare the real-world effectiveness in routine primary care of a novel once-daily investigational treatment with existing therapy for chronic obstructive pulmonary disease (COPD) and asthma (58, 59). Pre-license pRCT are large prospective clinical studies in which patients are randomised to two or more interventions, and then followed up according to the investigator physicians' usual practice. They differ from other RCTs just because they measure effectiveness (benefit the treatment produces) in routine clinical practice (59, 56, 57).

The Salford Lung Study is an open-label phase III pRCT in which Patients are randomised to receive either a continuation of their usual treatment or a novel once-daily Dry-Powder Inhaler (DPI) containing a combination of a new inhaled steroid and a new long-acting β-agonist (LABA) - fluticasone furoate/vilanterol (FF/VI) – Ellipta® (59, 56, 57).

After randomisation, patients receive 'usual' care for 12 months by their own general practitioner (GP), practice nurse and community pharmacist. In this way, community pharmacies are taking part in a phase III clinical trial. All community pharmacies in the Salford area of Greater Manchester have been given the chance to contribute to this clinical effectiveness trial developed by GlaxoSmithKline (GSK) (57).

GSK has paid for over 500 pharmacists, dispensing staff and counter assistants to be trained according to Good Clinical Practice requirements for the conduction of clinical trials. This training encompasses to handle the investigational treatment and complete the necessary labelling and record keeping. Pharmacy staff has been explained to treat patients in the trial arm as they would a normal patient, meaning no extra patient reviews

or counselling are required as part of the study. On the other hand, the staff is expected to take care and report any adverse reactions. Moreover, although patients who are allocated to the study therapy will be trained how to use the new inhaler by a practice nurse, community pharmacies in the area are also equipped with a placebo inhaler so pharmacists can demonstrate inhaler technique to the trial participants, if necessary (57).

The primary outcome for COPD is the rate of moderate and/or severe exacerbations. In the asthma study, the primary outcome is an improvement in asthma control (Asthma Control Test). A full regulatory package for FF/VI is under consideration by the European Medicines Agency, and at the time of the study's initiation, extensive efficacy and safety data were already available for more than 6400 patients from completed RCTs (59, 60).

Effectiveness and safety data are monitored and collected in near-real time using an electronic health record, minimising the number of patient visits required. GPs prescribe as usual, patients order and collect repeat prescriptions in their usual way and their study medication from their usual community pharmacist (59, 60).

This study faced some design challenges. The key objectives in designing and executing the Salford Lung Study were: enable collection of data with minimal disruption to normal care, enrol a large proportion of the local patient population, provide appropriate safety monitoring and meet all ethical and regulatory requirements. In the study's planning stages, the study sponsor and partners took advice from independent experts, including the Medicines and Healthcare Regulatory Authority (MHRA), the National Institute for Health and Care Excellence (NICE) and the National Institute for Health Research (NIHR), as well as the National Research Ethics Service Committee NorthWest, Greater Manchester South (59, 60).

The need of rigorous safety monitoring of phase III trials is provided in the context of usual care by remote monitoring using the Salford Integrated Record (SIR). Formal study visits are only required at baseline (consent and randomisation) and at the end of the study. Telephone calls every 3 months act as a 'safety net' if there has been no other contact between a patient and their GP (59, 60).

The first patients were enrolled for COPD study in April 2012 and for asthma study in December 2012. By mid-October 2013, more than 2000 patients gave consent and 1600 patients were randomised in the COPD study, on schedule for a target of 2800 by end of March 2014, with first results expected on second quarter of 2015. The asthma study recruitment is now accelerating, and likely to be complete 6 to 12 months later (59, 60).

The study execution has required intensive collaboration across the National Health Service, with the NIHR, MHRA, Ethics Committee, Academia and Industry. The creation of an effectiveness study environment in Salford serves as a benchmark for other initiatives, including pharmacovigilance and phase IV studies, to collect data from primary and secondary care anywhere in the UK. (59, 60) Such initiatives redesign the future of clinical trials and meet the demand for value-based medical evidence.

5. CLINICAL RESEARCH – THE PORTUGUESE REALITY

The possibility of conducting clinical research in Portugal involves interaction of various stakeholders. The majority of clinical trials in Portugal are promoted by multinational pharmaceutical companies of Research & Development (R&D).

However, the number of submitted clinical trials in Portugal between 2006 and 2012 fell by 26%, from 160 to 118 studies (10). The decrease in the number of clinical trials being performed in Portugal is revealing data from a progressive loss of competitiveness.

In this context, it is necessary to recognize that there is an opportunity to improve and promote the necessary communication between all stakeholders.

Community pharmacies constitute themselves as a possible partner in this scenario.

5.1. PORTUGUESE AUTHORITIES

5.1.1. INFARMED

When starting this work, the conduction of clinical trials on medicinal products for human use was regulated by Law No. 46/2004, of 19th August. (61) According to this law, and Infarmed procedures, the submission of a Clinical Trial Application (CTA) to Infarmed should be done in a mixed format (paper and CD-ROM) (62).

The information to be sent to Infarmed considering a CTAs and any changes thereafter shall be provided in electronic format as set out in the respective Instructions to Applicant. This format allows the automatic integration of this information in support of the assessment system in the Institute, optimizing the management, access, and archiving of processes throughout product's lifecycle. These instructions are the framework for organizing the elements in electronic format (CD-ROM) to submit to Infarmed and the procedure for the respective use. The indicated structure should not be changed and names assigned to each folder should be respected. (62)

Infarmed conducts inspections to clinical trials conducted in Portugal, as well as in other countries (European Union and third countries). These actions seek to verify compliance with Good Clinical Practice in the conduct of clinical trials, verification of compliance with Good Manufacturing Practice (GMP) for medicinal products, verification of Good Laboratory Practice (GLP), where applicable to clinical trials, as well as other rules and legal provisions in accordance with national and European Community legislation. Inspection activities involve sponsors, researchers, manufacturers, analytical laboratories and others, as well as any site directly or indirectly related to clinical trials conduction (63).

5.1.2. CEIC

Clinical research follow ethical references to promote the respect of all human beings, protect their rights and health, especially those submitted to clinical research. Ethics Committees have an essential role in the protection of subjects (64).

CEIC (*Comissão de Ética para a Investigação Clínica* – Ethics Committee for Clinical Research) was established by Law No. 46/2004 and it is guided not only by legal standards, but mainly by ethical principles aiming the respect of human rights (64).

According to Law No. 46/2004, of 19th August, CEIC is an independent organism, constituted by individuals related to health and other activity areas, whose mission is to ensure rights, safety and well-being protection of the participants in clinical trials, through the issue of an ethical opinion on the submitted clinical trial protocols. In order to meet this objective, CEIC makes a preliminary assessment monitoring of all clinical trials of medicinal products for human use. In this context, CEIC evaluates (65):

- relevance and design of the research protocol;
- risk-benefit profile of the intervention;
- ability of the research team;
- human and material resources available in research centres;
- compensation;
- insurance;
- amounts and terms of payment for researchers and participants;
- methods of recruitment;
- circuit and accessibility of experimental medicinal product;
- guarantee of volunteers' autonomy - particularly regarding the nature and adequacy of the information to be provided and the procedure for obtaining informed consent.

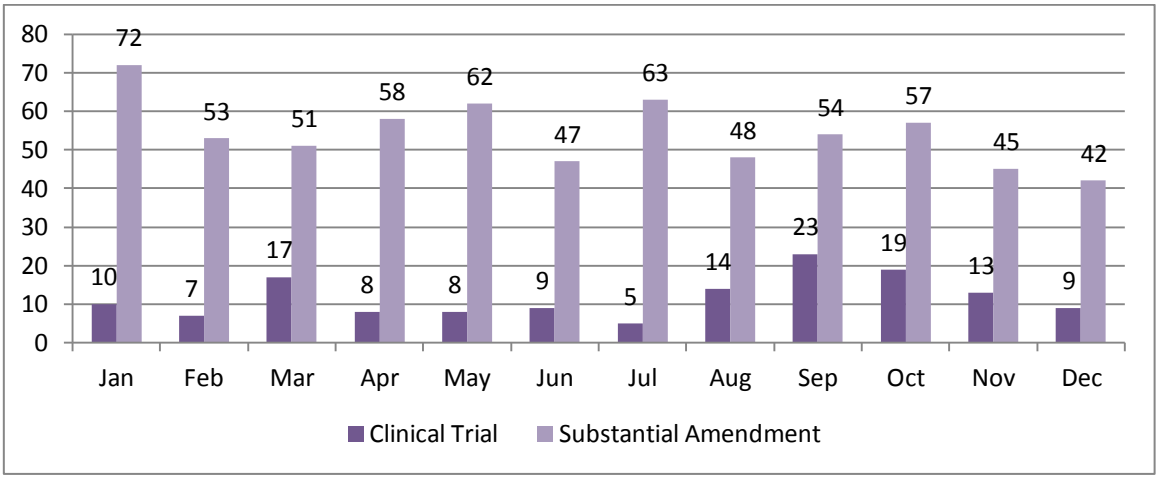

Figure 13. Number of Submissions to CEIC in 2013 (N=794) (adapted from (66)).

Figure 13 shows the total submissions to CEIC in 2013. Total submissions were calculated considering the number of total submitted processes to CEIC during the corresponding reported period (year 2013), and excluding cancelled processes (66).

Table 3 shows the number of days to issue a final opinion by CEIC. This number of days was calculated considering the period between the date of submission and the date of issuing the letter of plenary deliberation (excluding the time used by the sponsor for additional clarifications); total time for issuing an opinion included the time used for additional clarifications (66). This is an important delay issue concerning clinical trials initiation in Portugal.

Table 3. Descriptive Statistics about the time (days) to issue the final opinion, per type of application, in 2013 (adapted from (66)).

Type of Application										
	Substantial Amendment					Clinical Trial				
	Average	**Median**	**Minimum**	**Maximum**	**N**	**Average**	**Median**	**Minimum**	**Maximum**	**N**
1st Quarter	27.8	27	5	65	124	44.3	38	18	73	31
2nd Quarter	30.3	28	7	96	150	45.1	41	19	97	28
3rd Quarter	26.3	25	7	59	148	43.1	41	20	76	19
4th Quarter	27.9	27	5	61	138	38.8	36	13	75	30
TOTAL	**28.1**	**27**	**5**	**96**	**560**	**42.0**	**39**	**13**	**97**	**108**

The graphics presented in Figure 14 show the proportion of favourable and unfavourable opinion issued by CEIC in 2013. Figure 15 show the number of opinions issued by therapeutic area (66)

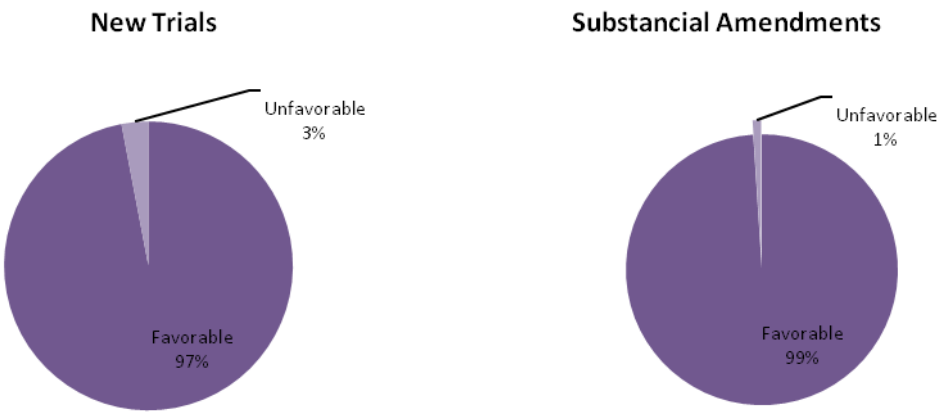

Figure 14. Favourable and Unfavourable opinions (% of total) (New Trials, N= 108; Substantial Amendments, N=559) (adapted from (66)).

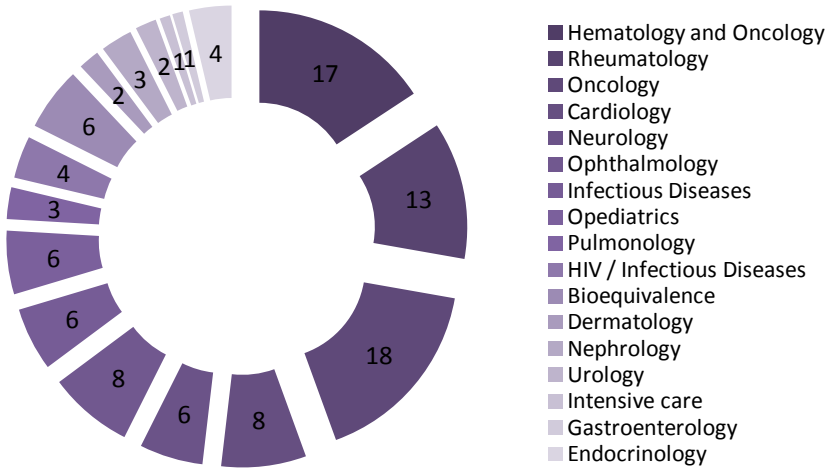

Figure 15. Number of opinions (Clinical Trial) by Therapeutic Area (N=108) (adapted from (66)).

With the entry into force of the new Law of Clinical Research (Law No. 21/2014, of 16th April) the role of CEIC is strengthened. It is expected that the statistics of time for opinion's issue come down in the forthcoming years, with the reduction of the deadline imposed by Law (67).

5.1.3. CNPD

The National Commission for Data Protection (CNPD) is an independent administrative authority. Generally, it supervises and monitors the processing of personal data in strict respect for human rights and freedom and guarantees protected in the Constitution and the law. The Commission is the National Supervisory Authority for Personal Data. Rights relating to the use of information technology are enshrined in the Constitution and developed by the Data Protection Act (68).

CNPD issued a Deliberation regarding research studies on health (*Deliberação nº227/2007*). CNPD stated that this kind of studies use various designations related to different objectives, methodologies and categories. This Deliberation relates to observational or epidemiologic studies, retrospectives and/or prospective (69).

The processing of data in order to perform health research studies focus on sensitive data and are therefore subject to control, according to paragraph a) of 28th article of Data Protection Law. In this way, these studies could not be performed before CNPD's prior authorisation. CNPD assess whether the treatment is according to data protection principles. Moreover, personal data used should be adequate, relevant and not excessive regarding its goal (69).

The following kind of data should be proved deemed necessary for the continuation of the study (69):

- Identification data;
- Health data (Clinical history/medication/exam results)
- Familiar history (health information/genetic information)
- Personal habits;
- Data related to professional activity;
- Data related to clinical study.

On the other hand, CNPD has also issued a Deliberation specifically for clinical trials (*Deliberação nº333/2007*). This Deliberation imposes not only scientific and technical requirements but also legal, juridical and ethical requirements to clinical studies. Clinical Trials Law (Law No. 46/2004, of 19th August) obliges as a minimal condition that patients' protection is guaranteed through right to privacy and protection of personal data of individuals, in accordance with their legal systems. (70)

5.2. Circuit of the Experimental Drug

In Portugal, "pharmaceutical act" is defined in the legislation (Decree-Law No. 288/2001, of 10th November) as (71):

- Development and preparation of the pharmaceutical form of medicines;
- Registration, manufacturing, control of medicines of human and veterinary use and of medical devices;
- Quality control of drugs and medical devices in laboratory of quality control of medicines and medical devices;
- Storage, conservation and wholesale distribution of medicines for human and veterinary use and of medical devices;
- Preparation, control, selection, acquisition, storage and dispensation of medicines of human and veterinary use and of medical devices in community pharmacies, hospital pharmaceutical services and public and private pharmaceutical services of any other entities;
- Preparation of antiseptic solutions, disinfectants and intravenous mixtures;
- Interpretation and evaluation of medical prescriptions;
- Information and consultation on medicines for human and veterinary use and on medical devices, in order to promote its correct use subjected, or not, to medical prescription, next to healthcare professionals and patients;
- Accompaniment, vigilance and control of distribution, dispensation and use of medicines of human and animal use and of medical devices;
- Drug monitoring, including determination of pharmacokinetic parameters and the establishment of individualized dosing regimens;
- Collection of biological products, execution and interpretation of clinical analysis and determination of serum levels;

- Execution and interpretation of toxicological, hydrological and bromatological analysis.

Pharmaceutical services are solely responsible for the investigational medicinal products and its circuit. The management process should be made to ensure safety, accountability, transparency and traceability.

Pharmaceutical services are responsible for the following processes (64):

(a) **Reception** – It should be ensured that study products (including placebo and concomitant medication) could only be delivered to pharmaceutical services where the clinical site is integrated, to the responsible pharmacist, or a deputy, designated by the director of service.
(b) **Storage and Dispensing** – The access to the investigational medicinal product could only be done by the responsible pharmacist or other designated pharmacist. The same goes for dispensing (directly to the patient or to nurses). Enhanced stocks in clinical services involved in the trial may be accepted, for drugs administrated in an urgent/emergent setting, although under supervision of the pharmaceutical services.
(c) **Preparation of IMP** – For drugs that require preparation procedures (cytotoxic, anti-infectives, nutrition, etc.) pharmaceutical services may use their own resources, meeting the applicable technical requirements.
(d) **Administration of IMP**
(e) **Devolutions** – The applicable procedures should be described and in accordance with the applicable legislation. It should be clear the mandatory collection of empty packaging and remaining medicines.
(f) **Investigator's Brochure (IB) and Authorisation** – Prior to trial initiation, up-to-date protocol should be available in the pharmaceutical services, as well as a copy of the authorization to start. Access, when needed, to the IB should also be ensured by the research team and other health professionals involved in investigational medicinal product circuit.
(g) **Forms** – Templates (forms) to be used for prescribing, dispensing and record the preparation and administration of the investigational medicinal product should be included.

According to point 1 of article 41º of Law No. 46/2004, of 19th August in healthcare institutions incorporated into National Healthcare Service, experimental drugs and devices used for its administration, as well as other medicines already authorized which are necessary to the trial, must be stored and dispensed by the hospital pharmaceutical services (61).

The circuit of the experimental drug is a technical and logistic responsibility of the pharmaceutical services of the sites where the clinical trials are being conducted. In 2013, CEIC has issued an opinion regarding the circuit of experimental drugs.

It was CEIC opinion that the principles established in article 41º of Law No. 46/2004 should be extended and generalized to all healthcare units, which are constituted as clinical trials sites (64).

According to point 4.6.2 of ICH GCP E6 Guideline where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institutions duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution (4).

With these assumptions, CEIC has outlined a set of guidelines for the implementation of the experimental drug circuit coordinated with the respective hospital pharmaceutical services (64):

- Minimum operating conditions: Pharmaceutical services in hospitals and healthcare units in which clinical trials are conducted should present a segregated area for the experimental drug, responsible for the integrity of the experimental drug circuit.
    - Physical conditions: These areas must have the following minimum physical requirements:
        - Proper space with restricted access;
        - Structures for storing confidential documents;
        - Suitable structures for storage of experimental drugs (separated by clinical trial; refrigerators with redundancy own power and audible alarms; separate quarantine area; calibrated monitors for temperature and humidity;
        - Access to the white area for handling drugs, when necessary;
    - Human resources: All pharmacists involved in clinical trials should be trained in Good Clinical Practice and Good Pharmaceutical Practice. The pharmaceutical services shall formally indicate the responsible for investigational medicinal products which should be responsible for managing samples

The documentation to be available to pharmaceutical services, before the start of the study should consist at least of (64):

- Protocol approved by regulatory authorities;
- Investigator’s Brochure and/or SmPC of the drugs involved in the study protocol approved by regulatory authorities;
- Copies of certificates of batch release of drugs and/or investigational medicinal products.

In case that these healthcare units are not provided with pharmaceutical services, as happens with Primary Healthcare Units, an alternative should be found.

OF (*Ordem dos Farmacêuticos* – Pharmacists’ Association) has also issued an opinion on this issue. According to them, CEIC proposed that when healthcare units are not provided with pharmaceutical services, the monitoring of the experimental drug circuit should be ensured by the pharmacist of the clinical trial monitoring company. However, OF proposed that Regional Health Administration create research teams for the Health Center, involving Community Pharmacies from the involving area, once they have training in clinical trials and facilities and procedures approved by Infarmed. Thus, similarly to the hospital

pharmacies, community pharmacies would ensure the circuit of experimental medicine as members of the research team, working in combination with the medical staff towards the patient ambulatory (72).

It is our understanding that community pharmacies when participating in a clinical trial in partnership with a primary healthcare unit might play the same role of pharmaceutical services in hospitals.

Community pharmacies may be the place where the investigational product is stored and dispensed to the patient; or, on the other hand, might just be the place of storage of the investigational product, being dispensed at the primary healthcare units.

The involvement of an external entity (with a different location) leads to the need of greater heed and accurate documentation of the entire circuit. Since the participation of community pharmacies in clinical research, particularly in clinical trials, led to a change in the circuit of experimental medicine as we know it (and described above).

The privileged location of the Portuguese community pharmacies in the community and its technical resources make them capable of performing this role in an integrated manner with the primary healthcare units.

However, also in this case as already happens in most clinical trials, feasibility should be assessed in a case-by-case basis.

5.3. Portuguese New Law on Clinical Research – Law No. 21/2014, of 16th April

During the elaboration of this work, Portugal saw approved a new Clinical Research Law (Law No. 21/2014, of 16th April) that would come into force on 16th June (67).

It regulates the clinical research considered as all systematic studies intended to discover or verify the distribution or the effect of health factors, conditions or health outcomes, processes of health and disease, performance, and, or safety interventions or provision of healthcare (67). This Law replaced the Law No. 46/2004, of 19th August known as Clinical Trials Law which approved the legal regimen applicable to the performance of clinical trials of medicinal products for human use (61).

Clinical Research Law covers clinical trials with medicinal products for human use and clinical research of medical devices. Once the scope of the new legislation is much larger than the previous Law of Clinical Trials, many concepts are revised to encompass all these types of research.

This Law also determines a great reduction in timeframes for approval. For example, the time to issue of opinion by Ethics Committee reduces from 60 to 30 days for new clinical trials and from 35 to 20 days for protocol amendments.

It also determines that the request for opinion shall be done through RNEC (*Registo Nacional de Estudos Clínicos* – National Register of Clinical Studies). RNEC is an electronic platform for the registration and disclosure of clinical studies, which promotes the interaction between all stakeholders in the clinical research field, facilitating and encouraging the development of high quality research for the benefit of patients as well as the dissemination of national clinical research to the general public, professionals and researchers. RNEC works next to Infarmed and it is coordinated by a commission constituted by a representative of Infarmed (presiding), a representative of CEIC and a representative of National Institute of Health Dr. Ricardo Jorge, designated by the member of the government responsible for the health sector (67).

The objectives of RNEC are as follow (67):

- Establish a public registry of clinical studies, researchers, clinical studies centres, sponsors, CEC (*Comissão de Ética Competente* – Competent Ethics Committee) opinions, publications, research instruments, while respecting the rights of the sponsor and the investigator in what concerns intellectual property;
- Provide information to support clinical studies in Portugal, throughout their various stages, including the various electronic forms for submission to CEC, Infarmed, and other entities;
- Identify relevant knowledge areas to each participant in clinical studies;
- Create a website with relevant information on clinical studies, clinical studies centres, reports and studies on clinical research in Portugal;
- Spread and promote training opportunities in clinical trials field;
- Foster collaboration among sponsors, investigators and centres of clinical studies;
- Promotion of public and private services in support of clinical studies as well as national resources to support research, including clinical registries, biobanks, and clinical and genetic databases, and centres of excellence;
- Promotion monitoring indicators of the various stages of the process, in particular relating to the submission, approval and implementation of the clinical studies;
- Provide ongoing evaluation of response capability of the authorities responsible for the approval and implementation of the clinical studies;
- Contribute to the internationalization of clinical research, providing supportive elements for performance of studies in Portugal addressed to researchers and foreign sponsors;
- Provide or, when not possible, state publications, presentations and reports arising from the realization of registered clinical studies;
- Provide the design, instruments of data collection of public domain and databases metadata, avoiding duplication of studies and fostering collaboration between researchers;
- Provide a public version of the database of clinical studies, mandatorily for clinical studies with direct or indirect financing from public funds, duly authorized by the

CNPD and respecting the rights of the sponsor and the investigator in what concerns intellectual property within three years after completion of the registered clinical study;
- Continually assess and monitor the performance and quality of clinical research in Portugal;
- Contribute to the promotion of literacy and the social dissemination of the role of clinical research;

Infarmed should assure the articulation of RNEC with database information, health and safety vigilance systems, as well as public registries of clinical studies and scientific repositories, promoting information standardization, interoperability and communication between them (67).

For the conduction of clinical studies, investigators and their teams, sponsors, monitors, CES and clinical studies centres shall be registered in RNEC. Likewise, the investigator or the sponsor should register the clinical trial or interventional medical device clinical study on RNEC prior, or at the same time, of the request for an opinion to CEC or the authorisation application to Infarmed. Publications, presentations and reports relating to clinical trials, shall be made available by the investigator or the sponsor within 30 days after their publication (67).

Portuguese New Law on Clinical Research (Law No. 21/2014, of 16 of April) (67), introduced the concept of qualified pharmaceutical service which is a service that has an authorisation for direct acquisition of medicines issued by Infarmed. This authorisation identify the responsible pharmacist, who should have good clinical practice training and ensure compliance with the requirements of storage and circuit of experimental drugs and medical devices used for its administration, as well as other authorised medicines. The qualified pharmaceutical service should also have an authorisation for direct acquisition of narcotic and psychotropic substances (if the pharmaceutical service handles this kind of substances).

According to this Law, pharmaceutical services are responsible for reception, storage, preparation, dispensation, collection and return or destruction of the medicinal product, having the duty to prepare a document describing the experimental drug containing circuit elements relating to the receipt, storage, dispensing and administration of the experimental drug.(67)

5.4. Studies Performed in the Portuguese Community Pharmacies Setting

In Portugal, the conduction of clinical trials in cooperation with community pharmacies is not yet a reality as well known as it was demonstrated above for other countries. A search

on clinicaltrials.gov for "community pharmacy" found 47 results . The same search in the European register of clinical trials (https://www.clinicaltrialsregister.eu) reveals just 1 result. The Portuguese portal of clinical trials, does not yet have this kind of information. However, it is expected that this would change with the implementation of the new Law of Clinical Research.

On the other hand, it is possible to verify that the Portuguese community pharmacies already play an important role in conducting observational studies in Portugal, notably by CEFAR (*Centro de Estudos e Avaliação em Saúde* - Centre for Health Evaluation & Research) (76).

An observational study was performed in seven Portuguese community pharmacies between October 2002 and July 2003. This study aimed to analyse and characterize demographic, clinical and therapeutic aspects, in a group of individuals with type II Diabetes. In this study, the methodology was based in a systematic selection of 150 patients for which an assessment questionnaire was implemented (77).

This transversal, observational and multicentre study measured blood glucose levels, blood pressure, body mass index, family history of Diabetes and drug intake. Each responsible pharmacist (after receiving specific training) administered the questionnaire presented in Figure 16 to the type II diabetics (77).

Pharmacy:_____
Pharmacist:_____

Variables	Data
Time to complete the questionnaire (hour/min)	Start/End
Date	
Name	
Telephone / Mobile phone	
Age (years)	
Sex (F/M)	
Weight (Kg)	
Height (m)	
Family history (Y/N/DK)	
Duration of diagnosis (years/months/weeks/days)	
Hypoglycemia(s) (if ever felt dizziness, tremors, visual changes, sweating, palpitations, dizziness or passed out) (Y/N)	
Opinion about Diabetes control (1.G; 2.R; 3.B)	
Self-monitoring (Y/N)	
Capillary glycaemia (cg), glycosuria (gu) or both (cg+gu) (Y/N)	
Fasting glucose (mg/dL) (at least 2hours fasting)	
Total Cholesterol (mg/dL)	
systolic blood pressure (mmHg)	
Diastolic Blood Pressure (mmHg)	
Antidiabetic (1)	
Antidiabetic Dose /day (1) (mg)	

Antidiabetic (2)
Antidiabetic Dose /day (2) (mg)
Antidiabetic (3)
Antidiabetic Dose /day (3) (mg)
Insulin (Y/N)
Antihypertensive (1)
Antihypertensive (2)
Antihypertensive (3)
Antidyslipidemia (1) etc

Figure 16. Questionnaire of registration of study variables (adapted from (77)).

B: bad; cg: Capillary glycaemia; DK: don't know; F: female; G: good; gu: glycosuria; M: male; N: no; R: reasonable; Y: yes

This data collection instrument included 3 types of variables: demographic (sex and age), clinical (capillary glycaemia, systolic and diastolic blood pressure, total cholesterol, occurrence of hypoglycaemia, self-monitoring, familiar history, diagnosis duration and opinion on disease control) and therapeutics (oral antidiabetic drugs and daily doses, antihypertensive drugs and antidyslipidemic drugs). This study was able to conclude that clinical variables of participant patients were not reasonable. This might not be a representative sample of the Portuguese population, but may be taken as a good indicator, for the analysed year (2003) (77).

Observational studies are a great tool to identify important health issues on the population and to find a way to overtake them. Portuguese community pharmacies may also have an important role on the development of this kind of studies, because they have access to a large population and proper knowledge about several diseases. Nowadays, the studies are considered to be of great importance since they can give us real world data.

6. THE NEXT STEP - APPLICATION OF A QUESTIONNAIRE

The lack of information concerning Clinical Research in Portuguese Community Pharmacies makes it necessary to assess the interest of Portuguese Community Pharmacies in participate in this kind of research. In this way, the survey established by Carr MB *et al.* (cf. Figure 17) might be of great interest (30). In their study, Carr MB *et al.* intended to assess the interest of American Pharmacy Services Corporation (APSC) independent community pharmacists in participating in a community pharmacy research network (CPRN) and to identify perceived barriers to participation in a CPRN.

(You may skip any question(s) that you do not want to respond to and you may stop answering questions at any time)

Section I – Demographic Information

1. How old are you? _____(years)
2. What is your gender? _____
3. How long have you been practicing pharmacy? _____(years)
4. How long have you been in community practice? _____(years)
5. How long do you plan to practice pharmacy? _____(years)
6. What degree in pharmacy did you complete (Check all that apply)
   - □ B.S.
   - □ Pharm. D.
   - □ M. S.
   - □ Other (please specify) _____
7. What is your position or title?
   - □ Staff pharmacist
   - □ Pharmacist in Charge
   - □ Owner
   - □ Other (please specify) _____
8. How many prescriptions does your pharmacy fill in a typical **week**? _____
9. How many full-time equivalent (FTE) pharmacists does your pharmacy employ? _____
   - □ Part-time equivalent (PTE) _____
10. How many certified technicians (full and part) are employed at your pharmacy? _____
    - □ Non-certified technicians (full and part) _____
11. How many hours is your pharmacy open per week? _____
12. How many employees staff the pharmacy at a give time? _____
13. Would you consider your practice to be in an urban setting or a rural one? _____

14. Please answer the following questions concerning the physical environment of your pharmacy:

	Yes	No
Does your pharmacy have a private counselling area (away from pharmacy staff and other patients)?		
Does your pharmacy have a semi-private counselling area (away from other patients)?		
Does your pharmacy have access to online drug information resources (I.e. LexiComp, MicroMedex, Epocrates, etc.)?		

15. Which of the following is the most common payer for prescription drugs in your pharmacy?
    - □ Cash
    - □ Medicaid
    - □ Other third-party payer

16. Which of the following services do you offer in your pharmacy (Check all that apply)?
    - □ Immunizations
    - □ Durable Medical Equipment
    - □ Disease State Management
    - □ Medication Therapy Management
    - □ Compounding
    - □ Health Screenings
    - □ Others_____

Section II – Community Pharmacy Research Networks: CPRNs are groups of pharmacists working together to answer community-based health community-based health care questions and translate research findings into practice.

17. Please indicate your level of agreement with the following statement: Community pharmacists play an important role in healthcare-related research.
    - □ Strongly agree
    - □ Agree
    - □ Disagree
    - □ Strongly disagree

18. How do you believe that participation in a Community Pharmacy Research Network would affect the quality of care that patients receive at your pharmacy?
    - □ Greatly improve quality of care
    - □ Somewhat improve quality of care
    - □ No impact on quality of care
    - □ Somewhat worsen quality of care
    - □ Greatly worsen quality of care

19. How do you believe that participation in a Community Pharmacy Research Network would affect your patient's perception of the care that they receive at your pharmacy?
    - □ Greatly improve the perception of care
    - □ Somewhat improve the perception of care
    - □ No impact on the perception of care
    - □ Somewhat worsen the perception of care
    - □ Greatly worsen the perception of care

20. How would participation in a Community Pharmacy Research Network affect your job satisfaction?
    - □ Major increase in job satisfaction
    - □ Slight increase in job satisfaction
    - □ No impact on job satisfaction
    - □ Slight decrease in job satisfaction
    - □ Major decrease in job satisfaction

21. Which of the following do you believe is a reasonable compensation for a pharmacist's participation in a Community Pharmacy Research Network?
    - □ $0
    - □ $10-$25 per hour
    - □ $26-$40 per hour
    - □ $41-$55 per hour
    - □ >$55 per hour

22. How important would the following be in influencing your decision to participate in a Community Pharmacy Research Network?
    - Having a research assistant provided by the network who will assist you in conducting research projects
      - □ Very important
      - □ Important
      - □ Somewhat important
      - □ Not important
    - Having another pharmacist relieve you from all other pharmacy activities while conducting research projects
      - □ Very important
      - □ Important
      - □ Somewhat important
      - □ Not important
    - Having the opportunity to be a preceptor for student pharmacists who would be able to assist in conducting research projects
      - □ Very important
      - □ Important
      - □ Somewhat important
      - □ Not important
    - Having an opportunity to suggest future research topics for consideration within the Community Pharmacy Research Network
      - □ Very important
      - □ Important
      - □ Somewhat important
      - □ Not important

23. If the Community Pharmacist Research Network provided a research assistant to assist in data collection, what do you believe would be your level of interest in participation in a Community Pharmacy Research Network?
    - □ Very interested
    - □ Interested
    - □ Not very interested
    - □ Definitely not interested

24. If the Community Pharmacy Research Network provided funds to pay for an additional pharmacist to conduct research projects, what do you believe would be your level of interest in participation in a Community Pharmacy Research Network?
    - □ Very interested
    - □ Interested
    - □ Not very interested
    - □ Definitely not interested

25. Rank the following order of importance (1=most important; 4=least important) in deciding whether or not you would participate in a Community Pharmacy Research Network

    ____Having the opportunity to participate in a study that may be published in a scholarly journal such as the *Journal of the American Pharmacists Association*

    ____Having the opportunity to impact the practice of community pharmacy and improve your independent pharmacy

    ____Having the opportunity to present the results of a Community Pharmacy Research Network study

at regional or national meetings

____Financial compensation for participation in a Community Pharmacy Research Network

26. Rank the following in order of importance (1=most important; 3=least important) to improving your satisfaction with your practice setting:
____Solving clinical unknowns

____Solving workflow issues

____Solving insurance issues

27. Would you be willing to work with elder adults on research to improve their prescription drug safety?
Yes____ No____

a) If **yes**, what degree of assistance would you be willing to provide. (Check all that apply)
____ Display a flyer
____ Distribute a flyer to patients
____ Patient screening
____ Patient referral into intervention program
____ Host a kiosk containing a computerized program for patient self-screening, self-referral, and/or brief computerized intervention delivery
____ Directly deliver a <1 minute brief-intervention
____ Directly deliver a <5 minute brief-intervention
____ Directly deliver a <10 minute brief-intervention

28. Would you be willing to help raise elder adult awareness about the risks of alcohol consumption and prescription drug safety?
Yes____ No____

29. Which of the following best represents your level of interest in participating in a Community Pharmacy Research Network?
□ Very interested
□ Interested
□ Not very interested
□ Definitely not interested
□ I do not know enough about Community Pharmacy Research Networks to respond to this

30. How many hours per week would you be **willing** to devote to participation in a Community Pharmacy Research Network?
_____ Hours per week

31. How many hours per week would you be **able** to devote to participation in a Community Pharmacy Research Network?
_____ Hours per week

32. What is the biggest limitation that would keep you from participating in a Community Pharmacy Research Network?

33. Are you interested in learning more about opportunities to participate in a Community Pharmacy Research Network in the future?
Yes____ No____

Figure 17. Community Pharmacy Research Network Survey (adapted from (30)).

FTE: full-time equivalent *PTE: Part-time equivalent*

To apply this survey to the Portuguese reality, some issues should be taken into consideration. It is necessary to translate, adapt and validate this survey to the Portuguese community pharmacy population. The methodology for this task is proposed below.

The translation of this questionnaire into Portuguese (of Portugal) language would involve running two panels: a bilingual translation panel and a lay translation panel aiming to produce the most appropriate version of the survey in Portugal's Portuguese (78, 79).

The objective of the bilingual translation panel is to produce the first translation of the survey. This panel would contain five or six individuals, who are fluent in both English and Portuguese, with the Portuguese as their first or primary language. There is no need to be medically trained or professional translator. As far as possible, there should be approximately equal numbers of men and women and they should vary in age. The ideal method of running this panel is to use a computer attached to an overhead projector. The original survey is projected and one person will type in the Portuguese language under the English original. All members of the panel are then able to see the source item together with alternative translations. The group can then decide which one (or more) of the translations should be retained for consideration by the lay panel. The same method should be used to produce the questionnaire instructions in the Portuguese language (78, 79).

A lay panel would be required in order to ensure that the level of language used is appropriate for those who will then complete the survey. Since bilinguals often use somewhat different words or phrases from lay people, it is important to have the survey translated by a lay panel. This panel would only consider the translation produced by the bilingual panel. The original version would not be available to them. However, the group leader (the person who attended the bilingual panel) would ensure that the final version produced by the lay panel has conceptual equivalence to the original version. The lay panel should be able to see projected the Portuguese language item (or alternatives) and they should discuss the wording of the items and decide whether these are acceptable or if changes are required to improve clarity and immediacy (78, 79).

It is helpful if a range of ages is represented in this group to ensure that the final measure is acceptable to all age groups. If the panel is "too young", modern phrases might be included that are less well understood by older people. If the panel is "too old" the wording may appear stilted or old fashioned. At the very least, there should be at least one younger and one older (post-retirement) participant. There should be approximately equal number of men and women present (78, 79).

To validate the obtained survey a sample of community pharmacies would be required to test the new language version. The application of the survey should be made on two occasions, two weeks apart, and should be standard in both time points.

Once there is a validated translation of the mentioned survey, it should be applied to almost all Portuguese community pharmacies. According to the obtained results, it would be possible to assess the interest of Portuguese community pharmacies in participating in clinical research, giving us the baseline to all the posterior work on this issue.

7. DISCUSSION

Many pharmacists feel disappointed with their non-challenging dispensing role because they thought that closer involvement with the population would make their work more pleasing. Many pharmacists think their skills are being under-used, feeling like "over-qualified distributors of medicines" and needing for new challenges (2).

In regard of clinical trials, studies have shown that pharmacists would be very willing to provide trial information to interested patients. Likewise, customers with better relationships with pharmacists were more willing to accept information about clinical trials. Nevertheless, only 25% of pharmacists were prepared to discuss this with a pharmacy customer (45, 48).

The reason more often referred by community pharmacies as the reason for not participating in a study was time constraints associated with the busy practice environment in many community pharmacies. Lack of time is always the reason referred by who decline to participate in a study (47, 39, 38, 19, 46).

There are some strategies that might be used to enhance study-site recruitment (47):

- Endorsement and initial contact by the state professional association partners;
- Rapid recruitment contact by pharmacist members of the study team who are supported by study staff dedicated to the consent process;
- Modest financial incentives for participating pharmacy personnel.

The environment in which a community pharmacy is inserted and their closeness to primary care enables it to be part of several clinical studies that seek to provide information and answer the clinical conditions most frequently found in the community.

In Portugal, it can be seen that the current paradigm of community pharmacy is mandatorily conducting to the development of new skills and services. The involvement of Portuguese community pharmacies in clinical research may be a path to strengthen the role of pharmacies in the community, the National Health Service and the pharmaceutical industry itself.

It can be noted that several stakeholders are needed to perform clinical research. In this way, it would be good to increase the participation of Portugal in clinical trials in order to generate sustained new jobs. Nowadays, even more than at any other time, this would have a positive impact in Portugal. Although more prescriptions are in the pipeline than ever before, community pharmacists face today unprecedented challenges. In the last two decades, prescription margins have been cut by more than 50%, and competition from mail order and large retail chains has intensified (45). There are several factors that make pharmacists more receptive to new ways for generating revenue, and their deepening relationships with patients make them an attractive clinical trial recruitment channel (45).

It was shown that clinical trials can benefit from pharmacists' involvement. A study examined this impact through a survey held 3 months after the display of in-store clinical trial educational materials and pharmacist outreach activities. It was found that 1 in 7 respondents spoke to their pharmacist or the pharmacy staff about clinical trials. 82% of pharmacists reported speaking with patients about clinical trials, and 78% thought that patients were interested in learning about clinical research. 47% of patient respondents were interested in participating in a clinical trial, and 48% were likely to recommend that a friend or family member look for ways to participate in clinical research. Nearly 4% of patient respondents chose to participate in a clinical research study after seeing educational materials in their pharmacies (45).

Thus, each time a pharmacist talks to a patient it is an opportunity for clinical trial education. The patient-pharmacist relationship enables community pharmacists to differentiate themselves from their competitors and give insights into various determinant factors whether a patient is a good candidate for a clinical trial (45).

This was showed on the McKesson StudyLink Program, selected by a sponsor to identify, recruit, pre-screen, enrol and compensate newly diagnosed migraine patients who were eligible only if they were new to taking the study medication and had recently taken this medication for the first time. The challenge of this issue relates to the fact that it refers to newly diagnosed patients. It is easy to use prescription data to identify large number of patients using the study medication, but not so easy to find those who were newly diagnosed (45).

Community pharmacies perceive that they are able to provide routine and specialized services that benefit the community. They are entities having staff with suitable knowledge and capabilities to contribute on clinical trials conduction. Moreover, cooperation from health professional, peer support, and funding are important facilitators for the development of new services (23). To perform clinical research in a community pharmacy setting it is important that subjects take their prescriptions always in the same trial pharmacy. In fact, this is similar from everyday practice for many people, as they tend to choose always the same pharmacy. Comprehensibly, temporary residents such as tourists and students would have to be excluded (13).

A study conducted in Portugal by PriceWaterHouseCoopers showed that clinical research activities would be of great impact for Portugal social and economical development. It was shown that clinical research would allow clinical trial participants an early access to new drugs and therapeutics before its marketing. In the meantime, physicians participating in clinical research would benefit of their training and continuous development, as well as medical practice would benefit with the rigorousness imposed by the clinical research methodology. The improvement of the clinical research approach would benefit the scientific development of the country and the creation of centres of excellence (10).

In the meantime, and of great importance in the current Portuguese situation, clinical research would reduce public expenses, since the treatment of patients participating in clinical trials are funded by the respective sponsor and the treatment prescribed and supported by the National Health Service is replaced.

At the same time, this would benefit the creation of new qualified jobs, since there is a need to reinforce human resources in clinical trial sites, pharmaceutical companies and CROs.

In this way, it would greatly benefit the Government in tax revenues, improvement of the sector trade balance with important stimulating role on the value chain.

This work intended to be an approach and verification of what is happening in other countries. As can be seen, much work has been done in this field in recent years. Therefore, an increased intervention of community pharmacists on clinical research is expected to be of relevant importance for the Portuguese Healthcare System. More studies shall be done to create a workable system.

The approval of the new Law of Clinical Research (Law No. 21/2014 of 16th April), is positioned as an incentive to the involvement of other entities, beyond hospitals, in conducting clinical research in Portugal. The Portuguese community pharmacies may well be included in this paradigm in several ways:

- Participation in the experimental drug circuit in clinical trials in health units;
- Facilitating Clinical Trials in Portugal, participating in education of the population about this issue.
- Conducting clinical studies in pharmacy itself, either through observational studies, or through interventional studies (with use of OTC drugs, for example).

In our view, the first step would be to raise consciousness among Portuguese community pharmacists to this reality, so that when establishing the system, there are capable, trained and sensitized professionals to this new strand of their work.

There are several studies that may be applicable to Portugal. First of all, it is important to apply a questionnaire to a representative sample of Portuguese community pharmacists in order to identify their interest to take part in clinical research. Carr *et al.* published the questionnaire used in their study (*cf.* Figure 17), which may be adapted for use in Portugal (30). In a subsequent phase, other studies may also be of great interest to be adapted to Portuguese reality. This is the case of the survey of Saini *et al.* on factors influencing Australian community pharmacists' willingness to participate in research projects and of Peterson *et al.* on attitudes of Australian pharmacists towards practice-based research (39, 34). There are several networks that may be used to spread this survey: it could be done through *Ordem dos Farmacêuticos* (OF) or *Associação Nacional de Farmácias* (ANF – National Association of Pharmacies), since it represents most of the Portuguese pharmacies.

First it is suggested to use the questionnaire of Carr *et al.*, since it would fit for purpose. As stated, this questionnaire would need to be adapted for Portugal. In this way, it is necessary to translate and validate this questionnaire into Portuguese.

Figure 18 shows the parameters of a Strengths, Weaknesses, Opportunities, and Threats (SWOT) analysis applied to our suggestion. A SWOT analysis is an established method for assisting the formulation of strategy analysis. (80) Strengths and weaknesses refer to

attributes with an internal origin and Opportunities and Threats refer to attributes of the environmental. As one could estimate, Strengths and Opportunities refer to something helpful to achieve the objective and Weaknesses and Threats refer to something harmful to achieve the objective.

Figure 18. SWOT analysis of Carr *et al*'s questionnaire application in Portugal

In this case, the possibility to evaluate the perception and acceptability of the Portuguese community pharmacies regarding clinical research and the ease of access to a broad network of pharmacies, are positioned as Strengths of the application of this questionnaire. In the same way, the need to be able to encourage all pharmacies to participate and that pharmacies are receptive to changing mindset in a time of economic constraints makes them the anticipated Weaknesses of this questionnaire. On the other hand, it can be found that the need for change felt in the pharmaceutical sector and the Portuguese community pharmacies in particular, as well as the New Portuguese Legislation on Clinical Research (Law No. 21/2014) that leads a space to conducting clinical research in other areas than just the hospital, appear as Opportunities in our case study. Research in Pharmacy is covered by this new law and the participation of pharmacists in clinical trials in primary health units are also one of opportunities achieving this investigation would foster. On the other hand, the period of economic crisis that Portugal is facing and lack of response by pharmacists seem to be the major Threats that could be found.

It was also an objective of the project to find what has been done in Portugal on this matter, but information on clinical trials performed within a community pharmacy setting is scarce. Nevertheless, it was noted that some observational studies are already practice in community pharmacies.

Portuguese community pharmacies and pharmacists mindset would only change if some proposals are offered. This work and the application of the questionnaire would awake community pharmacies to this reality which often might not occur, since it differs to nowadays common daily practice.

8. CONCLUSION

In the last years, community pharmacists moved from the traditional product supply role to a more interventional one in the community.

Nevertheless, many pharmacists continued to feel their capacities as underused. Pharmacists, by their basic training, have an enormous capacity for intervention in various fields on Health. Clinical research is one of them.

For pharmacists, determining whether to participate in a clinical trial boils down to two simple questions: Is this the right thing to do for my patients? Will this be worth my time? The answer to the latter will depend not only on the compensation received, but on the relationship-building opportunities that such programs can offer. Those pharmacists who recognize that these relationships can be a differentiating competitive advantage would be more likely to participate.

The high level of user satisfaction with the pharmacy is a mean for facilitating the recruitment/advice on clinical trials in community pharmacy. Conducting community pharmacy studies represents a range of difficulties. However, it is possible to design a pharmacy based trial in accordance with GCP Guidelines.

This study showed the international reality on this issue, in order to be the basis of further studies on this matter, in such a way to be applied to Portugal.

Nowadays, the Primary Healthcare Setting is getting more and more importance in Portugal. The Primary Health Care reform has great importance in the landscape of Health in Portugal. The starting point for this reform was the result of a low level of satisfaction of all stakeholders. This reform involves a set of supporting principles as decentralization, self-organization and responsibility for results, and contributed significantly to increase access to health care. In Europe, the need of greater investment in primary healthcare to enable health systems to fulfil all their potential to the benefit of patients has been considered. It can be noticed that the investment not only has to do with human resources and infrastructure, but also with education, research, training, and continuous quality improvement.

On the other hand, it is recognised that data about patients' use of medicines in normal clinical practice – Real World Data – is ever more important in decisions affecting patients' access to medicines. Studies that demonstrate the value of medicines and aid developing new practices in the healthcare system provide many benefits by maximising the use of resources, benefiting patients and their compliance with medicines' administration.

The conduction of randomised controlled trials is very expensive. In the other hand, the lower costs and simplicity of real world data studies is an advantage that has powered the relevance of such studies. It is estimated that the presentation of real world data would become even more important in decisions affecting access to medicines. The collection

and use of this kind of data can enable all parties to achieve their objectives and, ultimately, to maximise patients' health gains.

It has been shown that other countries have woken up to the need to include and integrate community pharmacies in this area. Recent reforms of the health system in Portugal, including the publication of the Portuguese Law on Clinical Research (Law No. 21/2014, of 16th April) demonstrate the intention to improve this kind of research on healthcare outcomes for patients. Portugal has many advantages in positioning itself as interesting on the development of clinical research. It would be helpful if we are aware that this paradigm shift is necessary and good.

This work intended to be guidance and a push for clinical trials performance in Portuguese community pharmacies setting. In order to increase pharmacist's interest in research and facilitate their involvement, there is a need to fully investigate the barriers and facilitators to this new role. It is suggested the application of the questionnaire applied by Carr *et al.* to assess community pharmacists' opinion on this matter.

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